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BEARING OF GENERAL NUTRITIONAL STATE ON ATHEROSCLEROSIS

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NEW YORK

MUCH attention has been directed toward the role that specific nutritional factors may play in the development of atherosclerosis in man. For example, the influence of the cholesterol content of the diet and the blood has been studied in great detail. There are, however, a number of observations that indicate that the general nutritional state of a person may have an important bearing on the formation of the atherosclerotic lesions. These observations may be divided into two categories: (1) those suggesting that obesity favors rapid and extensive development of atheromatous plaques and (2) those indicating that prolonged undernutrition may retard the formation of such lesions.

Chief among the first group are the extensive statistics of insurance companies,[1] in which it is shown that important clinical consequences of atherosclerosis (e. g., occlusion of the coronary artery and cerebral hemorrhage) occur more commonly in obese persons than in persons of average nutrition or in the undernourished. The most plausible explanation of this finding is that the atherosclerotic process is more advanced in the obese group. The alternative explanation is that the lesions themselves may not be more severe in obese than in other persons but that the extra mechanical burden imposed on the cardiovascular system by excessive deposits of fat in the tissues may lead to greater impairment of function.

Diabetes mellitus and arterial hypertension are two conditions that are widely held to predispose to the development of atherosclerosis. There is considerable evidence that both occur more commonly in per-

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1. (*a*) Dublin, L. I.; Fisk, E. L., and Kopf, E. W.: Physical Defects as Revealed by Periodic Health Examinations, Am. J. M. Sc. **170**:576-594, 1925. (*b*) Britten, R. H.: Physical Impairment and Weight, Pub. Health Rep. **48**:926-944, 1933. (*c*) Dublin, L. I.: The Influence of Weight on Certain Causes of Death, Human Biol. **2**:159-184, 1930. (*d*) Dublin, L. I., and Marks, H. H.: The Build of Women and Its Relation to Their Mortality: A Preliminary Report, New York, Metropolitan Life Insurance Company, 1938; Mortality of Women According to Build: Experience on Substandard Issues, ibid., 1938. (*f*) Ideal Weights for Women, Statist. Bull. Metrop. Life Insur. Co. **23**:6, 1942. (*g*) Ideal Weights for Men, ibid. **24**:6, 1943.

sons who are overweight than in those who are underweight.[2] In Cushing's syndrome, in which obesity is coexistent with both diabetes and arterial hypertension, a tendency for severe atherosclerosis to develop has been noted.[3] The part that obesity itself may play in producing the arterial lesions in these disorders has not been clearly elucidated. Joslin[4] attributed the severe atherosclerosis of diabetic patients to the associated obesity. This view is not accepted by other observers.[5] In hypothyroidism and myxedema, in which both diabetes and arterial hypertension are generally absent, there is a tendency toward obesity. Severe atherosclerosis has been reported as frequent in this condition.[6] Severe atherosclerosis was reported by Kuczynski[7] to occur at an early age among nomads of the Kirghiz Steppes. A high incidence of obesity occurs in this population, due to consumption of unusually large amounts of food. French and Dock[8] reported that, of 80 young soldiers dying of coronary arteriosclerosis, 73 were overweight. Finally, the incidence of obesity increases progressively with age in much the same fashion as the incidence of atherosclerosis itself. This association may be merely one of coincidence, but the possibility exists that some of the increase in atherosclerosis with advancing age can be attributed to overnutrition.

In parts of the world where poor nutrition is prevalent, a low incidence of atherosclerosis has been reported. This appears to be particularly true of China and some of the Central American countries. In China Oppenheim[9] and more recently Snapper[10] observed little atherosclerosis even in persons dying at an advanced age. Similar observations have been reported in Costa Rica.[11] My observations in

2. Obesity and Diabetes, editorial, J. A. M. A. **95**:202 (July 19) 1930. Wyckoff, J.: The Treatment of Arteriosclerosis, in Cowdry, E. V.: Arteriosclerosis, New York, The Macmillan Company, 1933, p. 570.

3. Heinbecker, P.: The Pathogenesis of Cushing's Syndrome, Medicine **23**:225-247, 1944.

4. Joslin, E. P.: Arteriosclerosis and Diabetes, Ann. Clin. Med. **5**:1061-1080, 1927.

5. Wilder, R. M.: Diabetic Arteriosclerosis, Internat. Clin. **2**:13-20, 1939.

6. Fishberg, A. M.: Arteriosclerosis in Thyroid Deficiency, J. A. M. A. **82**: 463-465 (Feb. 9) 1924. Bartels, E. C., and Bell, G.: Myxedema and Coronary Sclerotic Heart Disease, Tr. Am. A. Study Goiter, 1939, pp. 5-15.

7. Kuczynski, B.: Pathologische-geographische Untersuchungen in der Kirgesisch-dsungarischen Steppe, Klin. Wchnschr. **4**:39, 1925.

8. French, A. J., and Dock, W.: Fatal Coronary Arteriosclerosis in Young Soldiers, J. A. M. A. **124**:1233-1237 (April 29) 1944.

9. Oppenheim, F.: Review of One Hundred Autopsies of Shanghai Chinese. China M. J. **39**:1067-1076, 1925.

10. Snapper, I.: Chinese Lessons to Western Medicine, New York, Interscience Publishers, 1941, pp. 160 and 190.

11. Anitschkow, N.: Pathologische Anatomie und allgemeine Pathologie der Arteriosklerose, in Conférence internationale de pathologie géographique, Utrecht, 1934, pp. 44-97.

the latter country are in accord. At the Hospital San Juan di Dios in San José, Costa Rica, the majority of persons coming to necropsy are decidedly underweight. Ordinarily, no subcutaneous, mesenteric, omental, perirenal, peripelvic or epicardial adipose tissue is found. Even persons in the sixth and seventh decades at death usually have practically no atheromatous plaques in the aorta, the coronary arteries or other vessels. In China Oppenheim [9] noted that even in the presence of syphilitic aortitis there were no superimposed atherosclerotic plaques in the aortic intima. In the United States and Europe syphilitic aortitis and atherosclerosis are often coexistent. The view has been expressed that the syphilitic lesion ordinarily promotes the formation of intimal atheromatous plaques.

The low incidence of atherosclerosis in China is sometimes attributed to dietary factors [10] or to related arterial hypotension.[9] It is true that neither arterial hypertension nor diabetes is common in that country, but the degree of atherosclerosis noted at necropsy is apparently even milder than that observed as a rule in nonhypertensive and nondiabetic persons in the United States. The difference of mean systolic blood pressures in China and the United States is less than 10 mm. of mercury.[12] Therefore it seems doubtful that this slight difference could account for the variations in severity of atherosclerosis. It is also unlikely that specific dietary factors are involved. There is no reason to believe that two such divergent populations as the Chinese and the Costa Ricans consume exactly similar types of food.

Weiss and Minot [13] stated that there is some evidence that patients with chronic pulmonary tuberculosis may enjoy relative freedom from atherosclerosis. In such patients severe malnutrition is commonly present. In the examination of arteries of tuberculous patients at necropsies in the department of pathology at New York University little atherosclerosis has been found, particularly when severe undernutrition was present.

There has been no convincing demonstration that the state of nutrition is not related to the formation of atherosclerotic lesions. Rosenthal,[14] it is true, in an analysis of postmortem material found no relationship between body weight and degree of atherosclerosis, but his series included relatively few examples of obesity. It is also true that

12. Tung, C. L.: Relative Hypotension of Foreigners in China, Arch. Int. Med. **40**:153-158 (Aug.) 1927.

13. Weiss, S., and Minot, S. R.: Nutrition in Relation to Arteriosclerosis in Cowdry, E. V.: Arteriosclerosis, New York, The Macmillan Company, 1933, pp. 233-248.

14. Rosenthal, S. R.: Studies in Atherosclerosis. Chemical, Experimental and Morphologic: III. and IV. Roles of Cholesterol Metabolism, Blood Pressure and Structure of the Aorta; The Fat Angle of the Aorta (F. A. A.) and the Infiltration–Expression Theory of Lipoid Deposit, Arch. Path. **18**:660-698 (Nov.) 1934.

obesity is more prevalent in women than in men, yet clinical evidence of disease of the coronary or the cerebral arteries is less common in women. There is, however, no substantial proof that arterial lesions are less abundant in women. Rosenthal [14] found no striking sex difference in the incidence of atherosclerotic plaques.

It is not generally accepted that a relationship exists between nutrition and atherosclerosis. In a review on this subject written in 1933, Weiss and Minot [13] made the following statement: "There is no proof that overnutrition leads to atherosclerosis in man." In 1943 Wright [15] made essentially the same comment. There are a number of circumstances that make it difficult to establish a relationship between the two. Chief among these is the fact that the state of nutrition may fluctuate during different periods of a person's life. During many terminal illnesses there may be profound loss of weight. Prolonged periods of heart failure resulting from coronary arteriosclerosis itself may lead to striking depletion of fat deposits throughout the body. Obviously, the general state of nutrition in a given person is best evaluated during periods of health. However, the usual methods of measuring the extent of involvement of the arteries during life are unsatisfactory. Roentgenographic evidence of calcification of arteries may signify medial involvement in complete absence of the more important intimal lesions. For the same reason direct palpation of peripheral vessels may give erroneous impressions. Clinical evidence of impairment of the coronary, renal or cerebral circulation, if present, is a more reliable guide to the extent of the atherosclerotic process. But even this may be misleading. Postmortem examination may subsequently reveal a few plaques limited to isolated segments of the arterial system. These may be strategically located to cause striking impairment of function, but the clinical impression of widespread arteriosclerosis is not confirmed. Contrariwise, necropsy may reveal atherosclerosis throughout the arteries of persons who during life never exhibited any consequences of this disease.

Postmortem examination thus remains the most satisfactory method of determining the extent of atherosclerosis. However, the state of nutrition found at death may be the result of the terminal disease process, particularly if a chronic ailment such as tuberculosis, cancer or heart disease is present. Moreover, the clinical record as regards fluctuations in weight is frequently inadequate or unreliable. These defects complicate the evaluation of necropsy statistics when one tries to make accurate analyses of the relationship between nutrition and atherosclerosis, but they do not completely invalidate the use of such statistics, for the following reason: In practically all instances the state of nutrition at death will be either the same or poorer than it was prior to the

15. Wright, I. S.: Arteriosclerosis, in Stieglitz, E. J.: Geriatric Medicine, Philadelphia, W. B. Saunders Company, 1943, pp. 496-497.

onset of the final illness. There are few fatal illnesses that are associated with increased deposition of fat shortly before death. In other words, any change in nutrition that occurs with fatal disease is usually in one direction, namely, from a well nourished to a poorly nourished state. If this circumstance is taken into account, valid information can be obtained from the analysis of postmortem material.

If no relationship exists between nutrition and atherosclerosis and all other pertinent factors, such as age, sex, arterial hypertension and diabetes, are controlled, the incidence of atherosclerosis at autopsy should be about the same in obese, well nourished and poorly nourished groups. This will obtain no matter what the state of nutrition of the various persons in each of these groups may have been prior to the terminal illness. If a significant relationship does exist, variations in the incidence of atherosclerosis are to be expected in these three groups but will have to be interpreted with the effects of possible terminal changes in nutrition taken into account.

In the first place, the group that is found to be obese at necropsy will consist almost entirely of persons who were obese prior to the final illness. From this group will have been lost some who were formerly obese but who have lost considerable weight because of a cancerous growth, tuberculosis, severe arteriosclerosis itself or some other chronic disease process. There is no reason to believe that any selective loss of weight or absence of such loss will have occurred only in the obese persons with severe atherosclerosis. Therefore the degree of atherosclerosis found in those in whom obesity persists at the time of necropsy should be a fair approximation of the degree of atherosclerosis to be found in obese persons as a whole.

The group that is found to be within average limits of nutrition at necropsy will contain some members who were formerly obese and will have lost a large number of persons who, while of average nutrition for most of their lives, became malnourished shortly before death. If obesity favors the formation of atherosclerotic plaques, the addition of the formerly obese persons will increase the incidence of atherosclerosis in this group. If obesity retards the development of atherosclerosis, the opposite will hold true. In either case the difference in incidence of atherosclerotic lesions in truly obese and truly well nourished persons will be reduced by the inclusion of some formerly obese persons in the group with average nutrition as estimated at the time of death.

The group that is judged to be poorly nourished at the time of necropsy will contain some persons who were obese in health and a larger number who were of average nutrition prior to the final illness. If prolonged undernutrition retards the progression of atherosclerosis, the addition of these recently undernourished persons will raise the incidence of atherosclerosis in this group above that which actually obtains

in the presence of chronic undernutrition. If prolonged undernutrition increases the incidence of atherosclerosis, the opposite will hold true.

If both obesity and undernutrition have the same effect on the incidence of atherosclerosis—if, for example, both enhance the formation of atherosclerotic lesions—there will be some difficulty in the interpretation of the postmortem observations. The inclusion of a large number of previously normally nourished persons within the chronically undernourished group will lower the incidence of atherosclerosis below the true value. At the same time the introduction of a smaller group of formerly obese persons with a high incidence of atherosclerosis into the remaining group with average nutrition will raise the incidence of atherosclerosis slightly. In other words, the difference among all three nutritional groups as evaluated at necropsy will tend to be erased.

In each example cited, it will be noted that terminal loss of weight tends to reduce rather than to exaggerate or reverse any true differences in the incidence of atherosclerosis that might be related to the original state of nutrition. If such differences are not great, they may be entirely concealed by the changes that have occurred in the nutritional state as a part of fatal disease processes. It is possible that the failure to detect an obvious relationship between atherosclerosis and nutrition hitherto is explainable on this basis.

The study reported in this paper is based on findings in 1,250 necropsies performed at Bellevue Hospital, New York. Of these, 1,000 represent consecutive, unselected necropsies of persons 35 years of age or older at the time of death. Since they included an inadequate number of necropsies of obese persons, the series was enlarged by including the next consecutive 250 necropsies of persons 35 years of age or older who were obese.

MATERIAL AND METHODS

The series is divided into three groups according to the state of nutrition as evaluated at autopsy. The statement as to the general state of nutrition recorded in the protocol was generally accepted in making this classification. This was fortified by the estimated weight in comparison with the length and the general body build and also by the description of the deposits of fat found in various parts of the body. A measurement of the subcutaneous abdominal layer of fat was available in most instances, and a recent check indicates that this measurement is a good standard for evaluating the general state of nutrition. An abdominal panniculus 3 cm. or more in thickness was accepted as evidence of obesity. An abdominal subcutaneous layer of fat of less than 1 cm. when combined with depletion of deposits of fat in other parts of the body was accepted as an indication of poor nutrition. Some inaccuracy is unquestionably involved in this type of classification. This is probably particularly true in the group classified as being of average nutrition, since some of these may have been mildly overweight or underweight. The actual body weight was not available in many instances. This measurement by itself is not an infallible one in determining the state of nutrition unless one takes into consideration the body build and the degree of dehydration or of accumulation of excess fluids in the tissues and body cavities.

The patients of each nutritional group were reclassified by the degree of atherosclerosis present into the following categories: (1) those with no atherosclerotic lesions anywhere in the arterial system or only slight ones; (2) those with a moderate degree, and (3) those with severe and widespread lesions. Again the pathologist's estimate as recorded in the protocol was accepted. This simple method of measuring the extent of atherosclerosis is open to criticism, since it is based on the subjective interpretation of an unconcerned observer who in many instances made but casual reference to the condition of the arteries. The pathologist may be subconsciously influenced by the age or the clinical diagnosis in making an estimate of the extent of the atherosclerotic process. Lesions that in an elderly person would be called moderate in degree are sometimes called extensive if seen in a young person. If a clinical diagnosis of general arteriosclerosis has been made and if only a moderate degree is found at necropsy, the pathologist may be tempted to emphasize the discrepancy by calling the lesions rather mild. However, most of the grosser inaccuracies probably fall into the group classified as showing a moderate degree of atherosclerosis, since there is a wide range of lesions that may be so designated.

These data may be lacking in precision, but they at least have the virtue of having been recorded with complete detachment as regards a possible relationship between atherosclerosis and general nutrition.

As a further check, the incidence of atherosclerosis of the coronary arteries was tabulated separately. These vessels were chosen not only because they are frequently involved by atherosclerosis but also because they are examined at necropsy with considerable care. There are many instances in which there is a wide disparity between the degree of involvement of the coronary arteries by atherosclerosis and that of all other vessels. But the results obtained from analysis of the data on the incidence of atherosclerosis in relation to nutrition in each large group were essentially the same for the coronary arteries alone as for the arterial system as a whole. The data obtained from tabulations of the incidence of coronary arteriosclerosis will therefore be referred to in detail only when some noteworthy difference was observed.

RESULTS

Relation of Sex and Nutrition to General Atherosclerosis.—In table 1 is recorded the incidence of general atherosclerosis in men and in women

TABLE 1.—*Relation of Nutrition and Sex to General Atherosclerosis*

		Atherosclerosis						
		None or Slight		Moderate		Advanced		
	Nutrition	No.	%	No.	%	No.	%	Total
Men	Obese.....	39	23.1	62	36.7	68	40.2	169
	Average.....	107	40.8	100	38.2	55	20.9	262
	Poor.....	173	47.1	136	37.1	58	15.8	367
Women	Obese.....	69	30.5	83	36.7	74	32.8	226
	Average.....	53	48.2	34	30.9	23	20.9	110
	Poor.....	53	45.7	42	36.2	21	18.1	116

in each nutritional group. It may be noted that the incidence of atherosclerosis is practically identical in the sex subdivision of the poorly nourished group and that there is a higher incidence of severe atherosclerosis

in the sex subdivisions of the obese group. In obese men the incidence of severe atherosclerosis is two and a half times as great as in poorly nourished ones, and only one half as many of the obese men have little or no atherosclerotic change. In obese women the incidence of severe atherosclerosis is almost twice as high as in poorly nourished women. In every instance the incidence of atherosclerosis in the sex subdivisions with average nutrition is intermediate to the incidence in the obese and the incidence in the poorly nourished sex groups. In other words, the incidence of general atherosclerosis in a series of patients, if not in individuals, is directly proportional to the amount of adipose tissue deposited throughout the body. Obese women appear to have a somewhat lower incidence of severe atherosclerosis than obese men.

The incidence of atherosclerosis of the coronary arteries in relation to the state of nutrition is recorded in table 2. It will be noted that the incidence of atherosclerosis of these arteries alone, as was that of

TABLE 2.—*Relation of Nutrition and Sex to Coronary Atherosclerosis*

		Atherosclerosis						
		None or Slight		Moderate		Advanced		
	Nutrition	No.	%	No.	%	No.	%	Total
Men	Obese.....	54	32.0	46	27.2	69	40.8	169
	Average.....	123	46.9	90	34.4	49	18.7	262
	Poor.....	220	60.0	101	27.5	46	12.5	367
Women	Obese.....	92	40.7	83	36.7	51	22.6	226
	Average.....	58	52.7	30	27.3	22	20.0	110
	Poor.....	69	59.5	33	28.4	14	12.1	116

general atherosclerosis, is approximately the same in the two sexes in the poorly nourished group. However, obesity in men appears to be a more important factor in increasing the incidence of atherosclerosis of the coronary arteries than obesity in women. The incidence of severe atherosclerosis is almost twice as high in obese men as in obese women. This suggests that other factors may be of importance in atherosclerosis of these particular vessels. For example, there may be some predisposing condition of the vessel wall in men that in the presence of obesity may favor the development of atherosclerosis. In all other respects the relationship between nutrition and atherosclerosis is essentially the same for the coronary artery by itself as for the arterial system as a whole.

Relation of Age and Nutrition to General Atherosclerosis.—The incidence of obesity increases with advancing age except in extreme old age. The relatively lower incidence of obesity late in life is due in part to the wasting and atrophy of tissues associated with senility and in part to the fact that the life span of obese persons is on the average shorter than that of persons of average nutrition or undernutrition.[1e] Nevertheless, it is possible that the relationship between nutrition and

atherosclerosis shown in tables 1 and 2 may be attributed to the inclusion of large numbers of old persons in the obese groups.

In table 3, in which the relationship of nutrition to general atherosclerosis is arranged by decades, this is shown not to be the case. The relationship within each decade is the same as that found for the entire series. The incidence of severe atherosclerosis is approximately two to four times as high in obese as in poorly nourished persons. It may be seen that the incidence of severe atherosclerosis is actually higher in the obese persons of 35 to 44 years than in the poorly nourished ones of 45 to 54 years. In fact, the incidence of severe atherosclerosis among the obese of any decade of life is greater than that among the poorly nourished persons of the succeeding age group. If the difference in incidence of atherosclerosis between obese and poorly nourished groups

TABLE 3.—*Relation of Age and Nutrition to General Atherosclerosis*

		Atherosclerosis						
		None or Slight		Moderate		Advanced		
Age, Yr.	Nutrition	No.	%	No.	%	No.	%	Total
35 - 44	Obese	26	55.3	17	36.2	4	8.5	47
	Average	54	77.1	14	20.0	2	2.9	70
	Poor	52	89.7	5	8.6	1	1.7	58
45 - 54	Obese	41	46.1	30	33.7	18	20.2	89
	Average	47	56.6	27	32.5	9	10.9	83
	Poor	50	56.2	33	37.1	6	6.7	89
55 - 64	Obese	27	22.9	47	39.8	44	37.3	118
	Average	44	44.0	39	39.0	17	17.0	100
	Poor	69	46.3	56	37.6	24	16.1	149
65 - 74	Obese	11	11.6	41	43.1	43	45.3	95
	Average	10	13.5	35	47.3	29	39.2	74
	Poor	46	37.1	53	42.7	25	20.2	124
75 and over	Obese	3	6.5	10	21.7	33	71.8	46
	Average	5	11.1	19	42.2	21	46.7	45
	Poor	9	14.3	31	49.2	23	36.5	63

be expressed in years, it may be said that obesity accelerates the development of severe atherosclerosis by about ten years. The figures in table 3 indicate that not only is the incidence of severe atherosclerosis high in obese persons but fewer obese persons escape with little or no atherosclerosis. With average nutrition the incidence of atherosclerosis is intermediate between that with obesity and that with poor nutrition. Within these two extremes the incidence of atherosclerosis appears to vary somewhat, so that in some instances it is close to that of obesity and in others close to that of poor nutrition. As already indicated, the age subdivisions designated as of average nutrition are more heterogeneous than those of the obese and the undernourished group, and less constancy is to be expected in the data derived from them.

Relation of Nutrition to General Atherosclerosis in the Nonhypertensive Group.—It is necessary to prove that the relationship between obesity and severe atherosclerosis indicated thus far is not influenced

by the inclusion of a large number of persons with hypertensive vascular disease in the obese group. Some difficulty is encountered in establishing the presence or the absence of prolonged arterial hypertension in the persons of any necropsy series. Many patients with hypertensive vascular disease are admitted to the hospital in shock or dying, and only low blood pressure readings are obtained. Even more important is the fact that after attacks of occlusion of the coronary artery the blood pressure of persons who formerly had hypertension may fall to within normal limits. In a few instances intracranial lesions may lead to a sudden elevation of blood pressure. In tables 4 and 5 the incidence of atherosclerosis for each nutritional group of men and women deemed to be free from hypertensive vascular disease is shown. The upper limits of normal blood pressure were placed at 150 systolic and 90 diastolic.

TABLE 4.—*Relation of Nutrition to General Atherosclerosis in Nonhypertensive Men*

		Atherosclerosis						
		None or Slight		Moderate		Advanced		
Age, Yr.	Nutrition	No.	%	No.	%	No.	%	Total
35 - 54	Obese	17	51.5	12	36.3	4	12.1	33
	Average	46	63.0	23	31.5	4	5.5	73
	Poor	67	71.3	24	25.5	3	3.2	94
55 - 64	Obese	7	25.0	13	46.4	8	28.6	28
	Average	26	50.0	20	38.5	6	11.5	52
	Poor	48	48.0	40	40.0	12	12.0	100
65 and over	Obese	2	6.7	13	43.3	15	50.0	30
	Average	9	18.7	24	50.0	15	31.3	48
	Poor	39	32.2	53	43.8	29	24.0	121
Total, 35 and over	Obese	26	28.6	38	41.7	27	29.6	91
	Average	81	46.8	67	38.7	25	14.5	173
	Poor	154	48.9	117	37.1	44	14.0	315

When one of these readings was slightly above and the other below the limit of normal and if cardiac hypertrophy was absent, the patient was classified as nonhypertensive. It is admitted that a considerable and unknown number of formerly hypertensive persons are included among the terminally nonhypertensive groups. It is unlikely, however, that the inclusion of these will alter the incidence of atherosclerosis to a great extent.

In men (table 4) the major observation is again confirmed, namely, that the incidence of severe atherosclerosis is considerably higher in persons who are obese than in persons poorly nourished, even when the known hypertensive persons are excluded. This holds true in each of the age subdivisions shown. An unexpected aspect is that up to the age of 65 the incidence of atherosclerosis in the nonhypertensive groups of average and poor nutrition is practically the same, whereas in those over 65 years of age the group with average nutrition has a higher incidence of atherosclerosis than has the poorly nourished group of

similar age. This suggests that in relatively young nonhypertensive men poor nutrition may not effectively retard or average nutrition enhance the development of atherosclerosis; on the other hand, hypertension may accelerate the development of atherosclerosis in relatively young men of average nutrition but may have little effect of this type in those of poor nutrition.

In nonhypertensive women (table 5) the difference in the incidence of atherosclerosis of the various nutritional groups is seen to be essentially the same as for men. In some of the age subgroups, in which the number of cases is relatively small, there is a certain amount of chance variation, but this is not enough to cast doubt on the validity of the major findings. The incidence of atherosclerosis is about the same in nonhypertensive women of average and of poor nutrition from 35 to

TABLE 5.—*Relation of Nutrition to General Atherosclerosis in Nonhypertensive Women*

		Atherosclerosis						
		None or Slight		Moderate		Advanced		
Age, Yr.	Nutrition	No.	%	No.	%	No.	%	Total
35 - 54	Obese	29	60.4	16	33.3	3	6.3	48
	Average	30	78.9	8	21.1	0	...	38
	Poor	24	77.4	6	19.4	1	3.2	31
55 - 64	Obese	11	30.6	16	44.4	9	25.0	36
	Average	6	46.1	4	30.8	3	23.1	13
	Poor	12	60.0	6	30.0	2	10.0	20
65 and over	Obese	5	13.9	14	38.9	17	47.2	36
	Average	3	11.5	13	50.0	10	38.5	26
	Poor	10	34.5	14	48.3	5	17.2	29
Total, 35 and over	Obese	45	37.5	46	38.3	29	24.2	120
	Average	39	50.6	25	32.5	13	16.9	77
	Poor	46	57.5	26	32.5	8	10.0	80

54 years of age. At more advanced ages those of average nutrition have a higher incidence than those of poor nutrition.

Relation of Arterial Hypertension and Nutrition to General Atherosclerosis.—In table 6 the relationship of nutrition to general atherosclerosis in the hypertensive groups is presented. Although all persons included in these groups had elevated blood pressure during their final illnesses, the duration of hypertension in many is not known. The difference in incidence of arteriosclerosis between obese and poorly nourished hypertensive persons is almost as great as between obese and poorly nourished nonhypertensive persons. Comparatively few poorly nourished women were found to have hypertension, particularly in the younger age groups. The incidence of atherosclerosis in these small groups probably has little statistical value. The incidence of severe atherosclerosis is found to be higher in hypertensive men with average nutrition than in those with poor nutrition. This is a point in contrast

to the findings in the nonhypertensive groups and supports the suggestion that hypertension may accelerate the development of atherosclerosis in both obese and average nutritional groups more than in poorly nourished ones.

By reference to tables 4 and 5 it may be noted, however, that the incidence of severe atherosclerosis is considerably higher in all hypertensive groups as compared with the corresponding ones without hypertension. It may be inferred, therefore, that the effects of hypertension in promoting the development of atherosclerosis are in good measure independent of the state of nutrition. In fact, all three factors that appear to be associated with the development of atherosclerosis—age,

TABLE 6.—*Relation of Hypertension and Nutrition to General Atherosclerosis*

			Atherosclerosis						
			None or Slight		Moderate		Advanced		
	Age, Yr.	Nutrition	No.	%	No.	%	No.	%	Total
Men	35 - 59	Obese	7	21.2	11	33.3	15	45.5	33
		Average	20	47.6	13	31.0	9	21.4	42
		Poor	11	42.3	11	42.3	4	15.4	26
	60 and over	Obese	6	13.3	13	28.9	26	57.8	45
		Average	6	12.8	20	42.5	21	44.7	47
		Poor	8	30.8	8	30.8	10	38.4	26
	Total, 35 and over	Obese	13	16.7	24	30.8	41	52.5	78
		Average	26	29.2	33	37.1	30	33.7	89
		Poor	19	36.5	19	36.5	14	27.0	52
Women	35 - 59	Obese	19	40.4	16	34.1	12	25.5	47
		Average	3	42.9	3	42.9	1	14.2	7
		Poor	5	50.0	3	30.0	2	20.0	10
	60 and over	Obese	5	8.5	21	35.6	33	55.9	59
		Average	11	42.3	6	23.1	9	34.6	26
		Poor	2	7.7	13	50.0	11	42.3	26
	Total, 35 and over	Obese	24	22.6	37	34.9	45	42.5	106
		Average	14	42.4	9	27.3	10	30.3	33
		Poor	7	19.5	16	44.4	13	36.1	36

obesity and hypertension—seem to operate independently of each other. In the presence of all three the incidence of severe atherosclerosis is particularly high. Three of every 5 obese hypertensive persons over the age of 60 have severe atherosclerosis; only 1 in 10 has slight atherosclerosis.

Relation of Heart Weight and Nutrition to General Atherosclerosis.—In some ways the weight of the heart at autopsy may be a more accurate measure of protracted hypertension than blood pressure readings obtained during periods of illness. But cardiac hypertrophy may result from other common conditions besides hypertensive vascular disease. These include valvular defects, myocarditis and the right-sided hypertrophy associated with pulmonary disease. Often systemic hypertensive vascular disease may be associated with these other types of heart disease, and it is difficult to determine how much the increase of weight of the heart is the result of the cardiac lesion and how much the result of the vascular

disease. Furthermore, even in the absence of hypertensive vascular disease and an intrinsic lesion of the heart, the weight of the heart varies considerably. At Bellevue Hospital it is not unusual to find hearts 450 Gm. in weight in large men in whom no evidence of hypertensive vascular disease has been elicited on repeated admissions to the hospital and in whom the heart shows no other abnormalities. Finally, it is possible to dissect away as much as 75 Gm. of adipose tissue from the epicardium of the obese subject.

Despite these drawbacks, most of which pertain to hypertrophied hearts, the incidence of atherosclerosis in each nutritional group is shown separately in table 7 for those persons with and without cardiac hypertrophy. This is done chiefly because it might be argued that enough persons who previously had arterial hypertension are inadvertently

TABLE 7.—*Relation of Heart Weight and Nutrition to General Atherosclerosis*

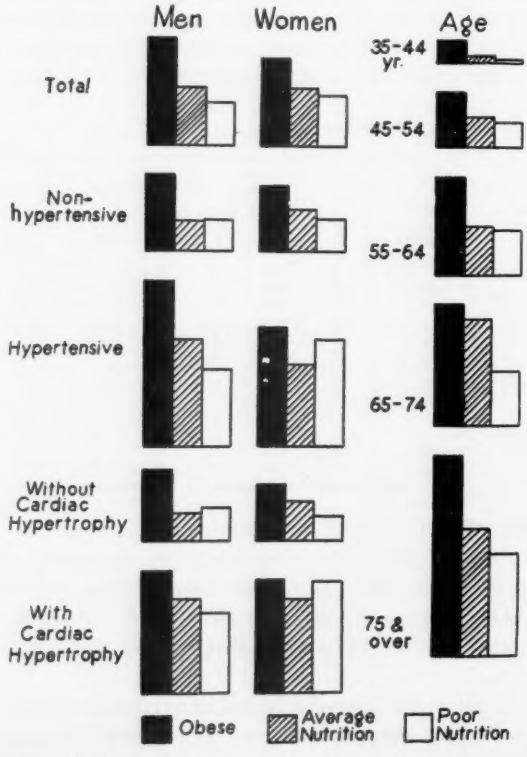
	Heart Weight, Gm.	Nutrition	Atherosclerosis: None or Slight No.	None or Slight %	Moderate No.	Moderate %	Advanced No.	Advanced %	Total
Men	Up to 400	Obese	9	37.5	8	33.3	7	29.2	24
		Average	53	54.6	38	39.2	6	6.2	97
		Poor	135	52.9	91	35.7	29	11.4	255
	400 and over	Obese	30	20.7	54	37.2	61	42.1	145
		Average	54	32.7	62	37.6	49	29.7	165
		Poor	38	33.9	45	40.2	29	25.9	112
Women	Up to 360	Obese	44	50.6	29	33.3	14	16.1	87
		Average	33	53.2	22	35.5	7	11.3	62
		Poor	41	54.7	28	37.3	6	8.0	75
	360 and over	Obese	25	18.0	54	38.8	60	43.2	139
		Average	20	41.7	12	25.0	16	33.3	48
		Poor	12	29.3	14	34.1	15	36.6	41

included among the obese nonhypertensive persons listed in tables 5 and 6 to raise the incidence of atherosclerosis in this group above the real value. The upper limits of normal heart weight are arbitrarily placed at 400 Gm. in men and 360 Gm. in women. No heart weights are excluded even when hypertrophy is obviously not the result of hypertension.

The main point under investigation is amply confirmed in table 7. There it may be seen that in both men and women without cardiac hypertrophy, and therefore presumably without prolonged arterial hypertension, the relative incidence of atherosclerosis in the obese group, the group of average nutrition and that of poor nutrition is about the same as indicated in tables 4 and 5, in which normal blood pressure readings obtained shortly before death were taken as the measure of absence of hypertension. It will be noted that the incidence of severe atherosclerosis is almost as high in the relatively small group of poorly nourished women with cardiac hypertrophy as in obese women with cardiac

hypertrophy. Examination of the clinical records revealed that at least 4 of the 15 poorly nourished women with both cardiac hypertrophy and severe atherosclerosis had lost much weight in the last few months of life. Inclusion of these among the small number of poorly nourished women with cardiac hypertrophy accounts for the falsely high incidence of severe atherosclerosis in this group.

Relation of Diabetes Mellitus and Nutrition to General Atherosclerosis.—The incidence of diabetes in persons 35 years of age or older on whom necropsy has been performed at Bellevue Hospital is only



The relative incidence of severe atherosclerosis in obese persons, persons of average nutrition and poorly nourished persons as influenced by sex, age, blood pressure and heart weight.

about 4 per cent. It is obvious that the inclusion of this small number among the 1,250 persons in this series will not appreciably alter the incidence of atherosclerosis in any one group. Diabetes, however, is fairly common in obese persons. Forty-two patients with diabetes (30 women and 12 men) are included among the 395 obese persons of

this series. Of these, 20, or almost 50 per cent, had severe atherosclerosis. If the diabetic group is omitted from the series, the incidence of atherosclerosis in nondiabetic obese men becomes: 23.7 per cent with little or no atherosclerosis, 37.8 per cent with moderate atherosclerosis and 38.5 per cent with severe atherosclerosis. Similarly, the incidence of atherosclerosis in nondiabetic obese women is: 33.3 per cent with little or no atherosclerosis, 35.9 per cent with moderate atherosclerosis and 30.8 per cent with severe atherosclerosis. Reference to table 1 will show that the incidence of atherosclerosis is not appreciably lower in obese nondiabetic persons than in the entire group of obese persons. It is still significantly higher in obese nondiabetic persons than in persons of average or pooor nutrition even if the diabetic persons are not excluded from the latter categories. It may be concluded therefore that the association demonstrated between obesity and severe atherosclerosis does not depend on the inclusion of diabetic persons in the obese group.

The relative incidence of severe atherosclerosis in each nutritional group as influenced by sex, age, blood pressure and heart weight is shown graphically in the chart.

COMMENT

It is an arresting fact that overweight is common in all the important conditions that are believed to be associated with the atherosclerotic process. The data furnished in this report indicate that overnutrition is in itself related to the development of atherosclerosis. There is also good evidence that poor nutrition may retard the formation of intimal lesions in old age and in the presence of hypertension. In nonhypertensive younger persons no difference in severity of atherosclerosis is observed in those of average and those of poor nutrition. The validity of the last observation is doubtful, as in both the latter groups the incidence of atherosclerosis has been artificially raised by the inclusion of formerly obese persons who became poorly nourished shortly before death.

From the figures cited in this report it would appear that obesity is less important than either high blood pressure or advanced age in promoting the development of atherosclerosis. However, it must be recalled that this study is based on the state of nutrition as observed at necropsy. It has already been indicated that the losses in weight that occur shortly before death will tend to reduce and conceal the nutritional factor in the incidence of atherosclerosis.

A crude estimate of the degree of nutritional change associated with fatal disease processes can be given. At death 30 per cent of the women over 35 years of age coming to autopsy at Bellevue Hospital are obese, 40 per cent are within average limits and 30 per cent are poorly nourished. A superficial survey of 1,500 visitors to the wards of Bellevue Hospital, who presumably were of the same background as the patients

themselves, indicates that, of middle-aged and elderly women, 60 per cent are frankly obese, 35 per cent within average limits and only about 5 per cent definitely underweight. These figures suggest that about one half of the obese women lose a large amount of weight before death and that undernutrition is six times as common among those who died. The nutrition of men over 35 years of age at autopsy is as follows: Only 10 per cent are obese; 40 per cent are of average nutritional status, and 50 per cent are poorly nourished. Corresponding figures for middle-aged and elderly male visitors to Bellevue Hospital are: 25 per cent obese, 65 per cent average and 10 per cent poorly nourished. In other words, more than half of the overweight group lose their obesity before death, and the incidence of poor nutrition is increased fivefold.

With these two sets of figures it is possible to estimate in a theoretic fashion the effects that change in nutrition at death might have on the true incidence of atherosclerosis as it is related to nutrition in health. For purposes of illustration, let it be assumed that 50 per cent of obese people, 25 per cent of persons with average nutrition and only 5 per cent of the undernourished over the age of 35 have severe atherosclerosis prior to illness. Let it be further assumed that two thirds of the obese people who lose weight because of wasting disease before death are brought by the loss of weight into the group with average nutrition and that in the remaining third the loss of weight has progressed to poor nutrition. In men the original true values of 50, 25 and 5 per cent of severe atherosclerosis in the respective groups will be altered by the weight changes to 50, 30 and 25 per cent. In women the same original values will be altered to 50, 38 and 30 per cent. In other words, a difference in incidence of severe atherosclerosis that was originally 10 to 1 between obese and poorly nourished persons has been reduced to 2 to 1 and 5 to 3.

This computation is based on the assumption that during a terminal period of a few months of poor nutrition no significant resorption or diminution of previously formed atherosclerotic lesions will occur. There is no evidence that the intimal plaques of adult human beings with atherosclerosis are reversible. It is likely, therefore, that the relationship between obesity and atherosclerosis is a much more striking one than the findings reported here indicate and that the state of nutrition is of great importance in the genesis of this disease.

It is obvious, nevertheless, that, like all the other factors known to be concerned in atherosclerosis, obesity is not essential for the development of the lesion. Almost 40 per cent of poorly nourished persons over the age of 75, from 30 to 40 per cent of all hypertensive persons with poor nutrition and even about 15 per cent of all poorly nourished nonhypertensive adults over the age of 35 have severe atherosclerosis at autopsy. It is not likely that the majority of these adults were ever

obese. Even when old age, hypertension and obesity are coexistent, almost 10 per cent may escape with little or no atherosclerosis.

It is also quite evident that obesity alone cannot be considered responsible for the development of atherosclerosis. This lesion is uncommon, for example, in obese persons under the age of 35. Even in older age groups, obese women appear to be less apt to have atherosclerosis than obese men. Finally, about one fourth of all obese persons over the age of 35 years show little or no atherosclerosis. Other conditions (e. g., predisposing changes in the arterial wall) must be fulfilled before overnutrition becomes a factor in the development of atherosclerosis, or one must suppose that there are different causes of obesity, only some of which are concerned in the atherosclerotic process. As a matter of fact, the data presented in this report merely confirm the existence of a relationship between nutrition and atherosclerosis; they do not afford any insight into the nature of this relationship. It might even be inferred that atherosclerosis leads to overnutrition, although this does not appear to be a plausible conjecture.

A certain amount of speculation over this relationship is perhaps justified. Newburgh [16] has shown that in obesity a disproportion between caloric intake and expenditure must inevitably be involved. In some instances of obesity the inadequate production of heat and energy due to sedentary habits or to intrinsic endocrine disturbances with lowered metabolic rate (e. g., hypothyroidism) may be chiefly concerned. In others excessive consumption of food is the predominant factor. It is likely that both excessive caloric intake and inadequate caloric expenditure are involved in many cases of obesity. Newburgh [16] finds that a relatively large consumption of food is required to maintain obesity. It is not inconceivable that the relationship between nutrition and atherosclerosis depends more on the excessive intake of food than on the amount of adipose tissue deposited throughout the body. The closer association between obesity and atherosclerosis in men than in women perhaps supports this contention, since the caloric requirements of men are generally stated to be higher than those of women. On the other hand, the association of atherosclerosis with myxedema and diabetes, since an excessive intake of food is not necessarily involved in these conditions, argues against this idea.

No matter what the cause of obesity may be in any individual case, it is logical that obesity involves the transportation of a large amount of fat from the alimentary canal to the tissues by way of the circulatory system. The development of atherosclerosis may conceivably result from a disturbance in this transportation. This is further supported by the

16. Newburgh, L. H.: Obesity: I. Energy Metabolism, Physiol. Rev. **24**:18-31, 1944.

discovery of Hirsh and Weinhouse [17] that the lipids initially deposited in the arterial wall have the same composition as plasma lipid. In a certain sense atheromatous lesions when they occur in conjunction with obesity may be considered as modified deposits of fat in unusual locations.

It must be admitted that numerous investigations have failed to reveal a constant increase of lipid content of the plasma in persons who have atherosclerosis. Most of these investigations ignore the fact that the unrestricted ingestion of food may be followed by temporary periods of hyperlipemia. Hetenyi,[18] it is true, noted less hyperlipemia in obese subjects following a high fat test meal than in undernourished ones, but others [19] have found significant alimentary hyperlipemia in obese subjects. It is reasonable to infer that when the consumption of food is excessive the alimentary hyperlipemia will be more sustained and greater in degree than when the consumption of food is limited. Even if alimentary hyperlipemia is not associated with hypercholesteremia in obese subjects as was suggested by Blotner,[19b] but denied by Oppenheim and Bruger,[19c] one may suppose that the intimal surfaces of the arteries of obese persons are exposed to lipid-rich plasma for longer periods than are those of persons with average or poor nutrition. It is likely that the explanation of the association between obesity and atherosclerosis resides in this inference.

SUMMARY

In a comparison of the incidence of various degrees of general atherosclerosis and of atherosclerosis of the coronary arteries at necropsy in 395 obese persons, 372 persons of average nutrition and 483 poorly nourished persons 35 years of age and older it was found that advanced atherosclerosis is about twice as common in the obese as in the poorly nourished group. The group with average nutrition has less severe atherosclerosis than the obese group but more than the poorly nourished one.

Almost twice as many of the poorly nourished group as of the obese group have little or no atherosclerosis at necropsy. The incidence of little or no atherosclerosis in the group with average nutrition is intermediate between that of the poorly nourished and that of the obese group.

17. Hirsh, E., and Weinhouse, S.: Roles of Lipids in Arteriosclerosis, Physiol. Rev. **23**:185-202, 1943.

18. Hetenyi, G.: Untersuchungen über die Entstehung der Fettsucht, Deutsches Arch. f. klin. med. **179**:134-150, 1936.

19. (*a*) Rony, H. R., and Levy, A. J.: Studies in Fat Metabolism: I. Fat Tolerance in Obesity, J. Lab. & Clin. Med. **15**:221-228, 1929. (*b*) Blotner, H.: Blood Fat Tolerance Tests in Malnutrition and Obesity, Arch. Int. Med. **55**:121-130 (Jan.) 1935. (*c*) Oppenheim, E., and Bruger, M.: The Effect of a High Fat Test Meal on Blood Cholesterol in Normal and Obese Subjects, Am. J. M. Sc. **205**:77-82, 1943.

The relationship demonstrated between the state of nutrition at necropsy and the degree of atherosclerosis is independent of age, sex, hypertension, heart weight and diabetes. When the series is divided into subgroups according to age by decades, sex, absence or presence of terminal arterial hypertension, absence or presence of cardiac hypertrophy, the differences in incidence of atherosclerosis between the nutritional groups are essentially unchanged.

There is some indication that in nonhypertensive persons under 65 years of age the incidence of mild, moderate and advanced atherosclerosis in average and poorly nourished groups is about the same.

Obesity appears to be a more striking factor in the development of atherosclerosis in men than in women. This is particularly true of atherosclerosis of the coronary arteries.

Although the analysis is based on the state of nutrition as observed at necropsy, evidence is presented to show that if the analysis had been based on the probable state of nutrition prior to the onset of the final illness the relationship between atherosclerosis and nutrition would be even more striking.

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NECROSIS OF RENAL PAPILLAE AND ACUTE PYELONEPHRITIS IN DIABETES MELLITUS

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ACUTE necrosis of the renal papillae is one of the most conspicuous changes that may be seen in the kidneys of diabetic patients. It is a part of acute pyelonephritis, which may be fulminating in type. Papillary necrosis occurs also in nondiabetic persons with chronic urinary obstruction. Recovery is only occasionally seen. Although it is an important complication of diabetes, it has received little attention in the medical literature or textbooks, especially in America. As the condition has been only partially reviewed in the past, a more complete résumé seems pertinent.

The association of necrosis of the papillae and diabetes mellitus was first emphasized by Günther,[1] in 1937. However, as he mentioned, reports of the anatomic lesion as seen both in diabetic and in nondiabetic patients go back much further. Friedreich's [2] report in 1877 was apparently the first. His patient was a man of 70 years who had prostatic disease, hydronephrosis and bilateral papillary necrosis. Some of the necrotic papillae had separated from the pyramids and perhaps had been eliminated in the urine. Friedreich thought the process to be one of necrotic sequestration, independent of inflammation and caused by pressure atrophy due to stasis of urine, plus the possibility that flattening of the papillae might cause angulation of the blood vessels and deprivation of blood supply.

Turner [3] reported 3 cases from 1885 to 1888, one of which (1888) was that of an obese white woman of 60 who had diabetes mellitus and

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1. Günther, G. W.: Die Papillennekrosen der Niere bie Diabetes, München. med. Wchnschr. **84**:1695, 1937.

2. von Friedreich, N.: Ueber Necrose der Nierenpapillen bié Hydronephrose, Virchows Arch. f. path. Anat. **69**:308, 1877.

gangrene of the left foot. Stoudensky's [4] report of 6 cases in 1899 included 2 previously reported by Chiari.[4a] In all the papillary necrosis was associated with obstructive lesions of the urinary tract. Four of the patients had calculi, and 2 had hypertrophy of the prostate. Chiari considered mechanical twisting of the papillae as an etiologic factor. In 1928 Kaufmann,[5] in his textbook, described "diphtheria" or necrosis of the papillae and mentioned the fact that they may become detached and even occlude the ureter. Schömer [6] in 1931 reported the lesion as capillary metastatic necrosis of the renal medulla. Among the 3 patients, 1 was diabetic, a man of 48 with abscesses of the mandibular angle, later observed at necropsy to be due to an infection of the nasal sinuses with Friedländer's bacillus. Septic temperature and hematuria were present. Two patients were nondiabetic. One was a 68 year old woman with carcinoma of the stomach and bacteremia without a known focus. Bacterial thrombi in the capillaries of the renal medullae in and around the areas of necrosis were outstanding. The other was a 48 year old man with abcesses of the skin and ulcerative endocarditis of the aortic valve. Schömer called attention to a predilection of the necrotizing process for localization in the centers of the pyramids.

In 1934 Grauhan [7] presented a report of 2 cases in which there was a unilateral calculus obstruction leading to infectious necrosis of the entire kidney. One patient was a 52 year old woman; the other, a 41 year old man. Both were nondiabetic. He discussed the relationship of pyonephrosis and impaired circulation to the necrosis. In the same year Foulon and Busser [8] observed ischemic necrosis of the renal papillae of the lower pole of a kidney of which retrograde pyelograms had been made with the aid of 10 per cent "collargerol." In the upper pole was a hypernephroma. They considered that the disease was probably due to

3. Turner, F. C.: A Kidney from a Case of Phthisis, Showing Mortification of the Apices of the Pyramids, Tr. Path. Soc. London **36**:268, 1884-1885; Necrosis with Softening in Pyramids of the Kidneys: Recent Endo-Pericarditis (Card Specimen), ibid. **37**:290, 1886; Necrosis of the Pyramids of One Kidney, ibid. **39**:159, 1888.

4. Stoudensky, A.: Ueber die Nierenpapillennekrose bei Hydronephrose, Ztschr. f. Heilk. **20**:459, 1899.

4a. Chiari, H.: Mitt. d. Wien. med. Doct. Coll., 1882, vol. 8, no. 12; Ueber den anatomischen Befund einer zwanzig Tage alten, inter partum entstandenen, in Heilung begriffenen, completen Uterusruptur, Prag. med. Wchnschr. **24**:283, 1899.

5. Kaufmann, E.: Pathology for Students and Practitioners, translated by S. P. Reimann, Philadelphia, P. Blakiston's Son & Co., 1929, vol. 2, p. 1364.

6. Schömer, W.: Capillarmetastatisch Marknekrosen der Nieren, Frankfurt. Ztschr. f. Path. **41**:265, 1931.

7. Grauhan, M.: Ueber die Entstehung von Pyonephrosen und entzündlichen Nierennekrosen, Ztschr. f. Urol. **28**:462, 1934.

8. Foulon, P., and Busser, F.: A propos des lésions rénales secondaires a la pyelographie rétrograde, Ann. d'anat. path. **11**:416, 1934.

compression of the blood vessels caused by the tumor, on one hand, and by distention of the pelves with collargol, on the other.

Günther [1] himself had observed the lesion in 10 specimens. Seven of these were from a series of 58 autopsies in which ascending suppurative pyelonephritis had been noted. Five of the 7 were from diabetic persons. Among 65 surgically removed pyelonephritic kidneys there were 3 with papillary necrosis complicating diabetes. Günther gave credit to Froboese for first emphasizing the relationship of papillary necrosis to diabetes mellitus. Froboese never published his observations. The same year Praetorius [9] observed "papillitis necroticans" in a 57 year old nondiabetic man. Also in 1937 Sheehan [10] reported a fatal instance of medullary necrosis of the kidneys in a nondiabetic 18 year old primipara in whom acute renal insufficiency developed post partum, associated with oliguria and arterial hypertension. She lived for nineteen days after the onset. Bacillus coli and staphylococci were present in the urine. At necropsy there was extensive necrosis of the papillae with commencing separation and microscopic healing at the line of demarcation. Sheehan expressed the belief that the necrotizing process, cutting across the collecting tubules, produced complete obstruction of the drainage of that segment; thus only small portions of unaffected renal tissue were able to function.

Alken's [11] report, in 1938, discussed 4 patients, all victims of diabetes mellitus and papillary necrosis, in 3 of whom the disease was unilateral and nephrectomy was performed. Only 2 of these were described in detail. One patient had complained of occasional fever and hematuria; a few days before admission to the hospital the patient had colicky pain, chills and high fever. There was almost complete loss of function of the left kidney, in contrast to normal function of the right. Retrograde pyelography revealed a large kidney with changes in the upper and the lower calices, composed of hazy outlines and irregular shapes. Nephrectomy was done and papillary necrosis noted. The other patient was a woman of 50 years whose chief complaint was hematuria. There was decreased function of the left kidney, Escherichia coli was present in the urine, and on a roentgenogram the contours of the upper calix were indistinct and contained a defect. The patient was treated conservatively but returned six months later because of renal colic of the left side. A papilla was passed in the urine, and the diagnosis of papillary necrosis was made histologically.

Alken emphasized the following points in clinical diagnosis: diabetes, decrease of renal function and roentgen findings, which are to be dis-

9. Praetorius: Papillitis necroticans bei schwerer chromischer Pyelonephritis, Ztschr. f. Urol. **31**:298, 1937.

10. Sheehan, H. L.: Medullary Necrosis of the Kidneys, Lancet **2**:187, 1937.

11. Alken, C. E.: Die Papillennekrose, Ztschr. f. Urol. **32**:433, 1938.

tinguished from those of tuberculosis and infiltrating tumor. However, the latter difficulty is present, as a rule, only in the early stages of papillary necrosis, when but one or two calices are involved. With advance of the disease and involvement of all papillae the evidence is against tuberculosis or neoplasm, which rarely involve all of the calices equally. He believed nephrectomy was indicated only in those patients in whom the disease was unilateral and of such severity that there was loss of renal function. With early diagnosis conservative treatment might be all that was necessary.

Mellgren and Redell [12] observed necrotizing pyelonephritis in 2 nondiabetic patients. One was a 63 year old woman who had had recurring bouts of pyelonephritis. Retrograde pyelography disclosed abnormalities of the calices on the left side. A contrast film revealed a mass which was thought to be a possible concretion. The involved kidney was explored and removed. Several days later symptoms referable to the right kidney developed, and the patient died several weeks later in uremia. In the left kidney at operation and the right kidney at autopsy there was diffuse papillary necrosis. The second patient was a 74 year old man who had prostatic hypertrophy, urinary retention and uremia. At necropsy there was a bilateral necrotizing papillary lesion. The blood sugar of this patient was normal.

The authors considered the predisposing cause to be deposition of a para-amyloid substance which acted to reduce the capillary blood supply, normally the poorest in the kidney. The precipitating cause, in their opinion, was a bacterial poison. In considering the relationship of diabetes to the disease, they thought that the deposition of a para-amyloid substance in the islets of the pancreas was similar to that in the renal papillae. In diabetic patients the para-amyloid substance, by pressure on vessels, would act as a special predisposing agent. They attached no importance to venous thrombosis. Among the characteristic roentgenographic changes, they included deformities and/or dilatation of the calices and separation of the papillary tips, leading to a mass of slough which might be called a concretion. Ring shadows in the roentgenogram were supposedly caused by sequestered papillae. The calices might communicate by small canals with the pelvis, simulating the appearance seen on the roentgenogram in renal tuberculosis.

Davson and Langley [13] published a report of a 28 year old woman with "papillitis renis necroticans" occurring as a terminal event in chronic pyelonephritis and uremia. There was no diabetes. In 1945

12. Mellgren, J., and Redell, G.: Clinical Pathology of Necrotizing Renal Papillitis, Acta chir. Scandinav. **84**:439, 1941.

13. Davson, J., and Langley, F. A.: Papillitis Renis Necroticans, J. Path. & Bact. **56**:327, 1944.

Eskelund [14] reported necrosis of the renal papillae following the use of a 25 per cent solution of sodium orthoiodohippurate for retrograde pyelography in a woman aged 55 who had acute and chronic pyelonephritis. In this country Harrison and Bailey [15] observed necrotizing pyelonephritis in 3 diabetic patients in whom there was no papillary necrosis.

In summation, then, papillary necrosis has been reported occurring in 13 diabetic and 20 nondiabetic persons, a total of 33. To this we add 50 unreported occurrences, 29 in diabetic and 21 in nondiabetic persons, bringing the total to 83.

As noted in foregoing paragraphs, there has been a lack of uniformity of opinion as to the proper nomenclature for this condition. The synonyms used include "papillary necrosis in hydronephrosis" (Friedreich [2]), "papillary necrosis of the kidney in diabetes mellitus" (Günther [1]), "papillitis necroticans" (Praetorius [9]), "diphtheria of the papillae" (Kaufmann [5]), "capillary metastatic necrosis of the renal medulla" (Schömer [6]), "necrotizing pyelonephritis" (Mellgren and Redell [12]) and "papillitis renis necroticans" (Davson and Langley [13]). As some choice has to be made by any author, we believe that the briefest descriptive term is best. At the Los Angeles County Hospital the resident staff has for a long time used the term "Günther's necrosis." Perhaps in due time Günther will be so honored. Only future authors can make that decision.

MATERIAL AND STATISTICS

For this report we have chosen our material from 859 necropsies of diabetic subjects (2.7 per cent) among 32,000 consecutive necropsies performed at the Los Angeles County Hospital between Sept. 23, 1924, and July 1, 1945. For comparison we have studied the acute infections of the kidneys in the remaining 31,141 nondiabetic subjects of the same necropsy series. We have not searched the surgical pathology records of the same period. In regard to material collected previous to 1941 we have depended on microscopic examination for diagnosis. Since that time we have personally supervised the collection of both gross and microscopic specimens. Among the 859 diabetic persons there were 107, or 12.4 per cent, in whom acute infection of one or both kidneys was the cause of death or contributed thereto. In this group of 107 with pyelonephritis there were 29, or 27.1 per cent, in whom a well circumscribed papillary to pyramidal necrosis was observed on gross or microscopic examination. In the remaining 78, necrotic areas were not seen in the papillae or, if present, involved only minor portions of one or more papillae. Minor degrees of renal infection were not included in this series of 107. There were 1,023 instances of acute pyelonephritis among the 31,141 nondiabetic subjects in the same series of 32,000 autopsies. In regard to

14. Eskelund, V.: Necrosis of Renal Papillae Following Retrograde Pyelography, Acta radiol. **26**:548, 1945; abstracted, J. A. M. A. **130**:1192 (April 20) 1946.

15. Harrison, J. H., and Bailey, O. T.: Significance of Necrotizing Pyelonephritis in Diabetes Mellitus, J. A. M. A. **118**:15 (Jan. 3) 1942.

the kidneys of 21 of these (2 per cent of the infected kidneys) we were able to make a diagnosis of papillary necrosis.

Certain inherent criticisms of such a study are obvious and should be mentioned. The gross descriptions of the disease recorded by the autopsy surgeons usually lacked sufficient detail for diagnosis previous to recognition of the process as an entity by the staff. Microscopic preparations of the kidneys often failed to include the papillae, even when the gross description would make one suspect necrosis. Sometimes no sections of kidney were saved, so that we had to depend entirely on written descriptions of the histologic observations for a diagnosis of acute pyelonephritis. Since we used only those cases in which the lesion was seen in

TABLE 1.—*Apparent Increase in Incidence of Papillary Necrosis*

Necropsies	Diabetic Subjects	Number with Pyelonephritis	Number with Papillary Necrosis
1st 10,000	201	20	3
2d 10,000	226	33	7
3d 10,000	360	45	12
Last 2,000	72	9	7
Total	859	107	29

histologic preparations and relegated all others to the group of pyelonephritis without necrosis, the number of those with necrosis, for both diabetic and non-diabetic groups, is probably much too small. The incidence per 10,000 autopsies (table 1) supports this hypothesis. When carefully searched for, the lesion was noted in a much greater percentage than our statistics indicate.

ACUTE NECROSIS OF RENAL PAPILLAE IN DIABETIC PATIENTS

Clinical Findings.—The clinical records of the 29 patients with necrosis of renal papillae are given in table 2 and summarized in table 3. In 26 patients (1 to 26 in table 2) the disease was of pyogenic origin. In 1 patient (27) healing had occurred, and in the remaining 2 (28 and 29) tuberculosis and actinomycosis, respectively, were the cause of the necrosis.

In attempting to analyze the data on the 26 patients with papillary necrosis of pyogenic origin it is noted that they can be divided into three groups, although there is some overlapping. In one group of patients there was a focus of infection elsewhere than in the urinary tract which resulted in septicemia and secondary involvement of the kidney. The second group consisted of diabetic patients whose renal lesion was the apparent result of infection confined to the urinary tract. The third group included those patients who entered the hospital in coma, presumably due to the papillary necrosis, and usually in uremia with or without diabetic acidosis, and who died after only a few days during which their disease followed a fulminating course. Detailed summaries of the observations on 1 patient from each group follow.

In group 1 (renal involvement secondary to infection elsewhere) there were 7 patients.

TABLE 2.—*Summ*

Patient	Age, Yr.	Sex	Cause of Entry to Hospital	Time in Hospital Before Death	Duration of Diabetes in Years	Complicating Diseases	Bacteriologic Results *	Carb Diox Com bini Pow
				Acute Papillary Necrosis				
1	35	M	Coma; hematemesis	14 hr.	13	Peptic ulcer; severe diabetic retinitis	.....	2
2	42	F	Burns of legs; peripheral neuritis	10 mo.	13	Carbuncle; hypertension; chronic pyelonephritis	P. M. kidney: Beta strep.	
3	62	F	Cellulitis of arm; gangrene of foot	5 mo.	12	.....	P. M. kidney: gram-positive cocci on smear	
4	71	F	Diabetes	25 days	20	Hypertension	.....	
5	43	F	Bacillary dysentery; diabetic acidosis	1½ mo.	New	.....	Blood: negative; P. M. kidney: E. coli	
6	51	M	Cirrhosis with ascites; hiccup	2 days	6	Generalized edema (Kimmelstiel-Wilson disease)	.....	
7	49	F	Diabetic coma	3 mo.	New	Abscess of thigh	Urine: E. coli; P. M. kidney: E. coli, alpha strep.	57
8	81	F	Coma	6 days	New	Generalized arteriosclerosis	.....	6
9	50	F	Urinary symptoms	2½ mo.	1	.....	Blood: E. coli; Urine: E. coli; P. M. kidney: B. proteus	
10	41	M	Carbuncle; diabetic coma	7 wk.	9	.....	Blood: Staph. aureus	
11	72	M	Coma	3 days	13	Prostatic hypertrophy; chronic pyelonephritis	Blood: negative	
12	63	F	Convulsions	2½ days	Several	Hypertension	P. M. kidney: E. coli	
13	55	E	Stupor	7 days	10	Hypertension, mild	.....	
14	58	F	Diabetic coma; chills and fever	4 days	New	.....	P. M. kidney: E. coli	
15	62	M	Urinary retention	4 mo.	1	Prostatic hypertrophy; paralysis of bladder due to injury of cord; perirectal and cutaneous abscesses; alcoholism	Blood: Staph. aureus	
16	68	F	Urinary symptoms	5 days	10	Hypertension	.....	
17	53	F	Diabetic acidosis	2 mo.	New	.....	P. M. kidney: E. coli	
18	74	M	Urinary retention (prostatic hypertrophy)	14 days	?	Auricular flutter	.....	
19	68	F	Carbuncle	6 days	1	.....	Blood: negative P. M. kidney: Staph. aureus	
20	63	F	Coma	12 days	3	Hypertension	P. M. kidney: Staph. aureus	
21	53	F	Diabetic acidosis; gangrene of toes	5 days	New	Hypertension, mild	P. M. kidney: E. coli	
22	68	F	Hematuria	5 days	14	Old hemiplegia; amputation of toe	P. M. kidney: E. coli, alpha strep.	
23	54	M	Generalized edema (Kimmelstiel-Wilson disease)	14 days	6	.....	P. M. kidney: Staph. aureus	
24	59	F	Diabetes	17 days	New	.....	P. M. kidney: Pseudomonas aerogenes, alpha strep.	
25	58	F	Diabetic coma	10 days	New	Gangrene of toes; pneumonia	.....	
26	46	M	Coma (uremic) due to chronic pyelonephritis (urethral stricture)	1 day	New	Meningovascular syphilis	P. M. kidney: E. coli	
				Healed Papillary Necrosis				
27	81	M	Diabetes; shortness of breath (Kimmelstiel-Wilson disease)	3½ mo.	New	Infected ulcer on leg	.....	
				Granulomatous Lesions with Papillary Necrosis				
28	57	M	Urinary symptoms; diabetes	32 days	5	Severe malnutrition	.....	
29	59	F	Urinary symptoms	3 mo.	New	.....	Blood: negative Urine: negative for acid-fast bacilli	

* P. M. kidney means postmortem culture of kidney.
† Carbon dioxide combining power is expressed in volumes per cent, taken within fourteen days of death.
‡ Nonprotein nitrogen is expressed in milligrams per hundred cubic centimeters of blood, taken within fourteen days of

Nonprotein Nitrogen ‡	Urine: Microscopic §: Albumin	Urine: Microscopic §: White Blood Cells	Urine: Microscopic §: Red Blood Cells	Treatment of Renal Lesion	Gross Pathologic Changes
				Acute Papillary Necrosis	
212	...	...	...	.....	Unilateral papillary necrosis with cortical abscesses; chronic pyelonephritis of opposite kidney
...	1+	4+	4+	.....	Bilateral papillary necrosis with partial sloughing and healing; chronic pyelonephritis (?); carbuncle; epidural spinal abscess; pulmonary abscesses
...	3+	...	...	.....	Bilateral papillary necrosis; no cortical abscesses; mild cystitis
...	1+	4+	...	"Urinary antiseptics"	Bilateral papillary necrosis; extensive cortical abscesses; purulent cystitis
...	2+	4+	...	.....	Unilateral papillary necrosis; bilateral pyelonephritis; acute cystitis and ureteritis; bilateral pyosalpinx and pelvic abscesses
...	2+	4+	Rare	.....	Bilateral papillary necrosis; no cortical abscesses; prostatic hypertrophy; uropathy due to infection and obstruction; portal cirrhosis
57	1+	4+	...	Ureteral catheters; "urinary antiseptics"	Unilateral papillary necrosis and chronic pyelonephritis due to ureteral kink
60	1+	4+	...	.....	Unilateral papillary necrosis and pyonephrosis due to ureteral kink; no cortical abscesses
248	1+	4+	...	Ureteral catheters; sulfanilamide	Bilateral papillary necrosis with sloughing; perirenal inflammation; acute cystitis and ureteritis; weight of kidneys, 600 Gm.
...	2+	4+	4+	Sulfapyridine and sulfadiazine	Bilateral papillary necrosis with abscesses throughout kidneys; carbuncle of neck; cellulitis of leg
70	1+	...	...	.....	Unilateral papillary necrosis; no cortical abscesses; benign hypertrophy of prostate with obstruction
150	1+	4+	...	.....	Bilateral papillary necrosis with cortical abscesses; acute cystitis and ureteritis
230	Trace	1+	...	Ureteral catheters; sulfathiazole	Bilateral papillary necrosis; acute ureteritis; coronary sclerosis; myocardial scars; hirsutism of face; adrenal hyperplasia; nodular goiter; bronchopneumonia
48	...	1+	...	.....	Unilateral papillary necrosis with small early cortical abscesses; mild acute ureteritis and cystitis; bronchopneumonia
90	4+	4+	4+	Retention catheter; sulfathiazole	Bilateral papillary necrosis; no cortical abscesses; benign hypertrophy of prostate; gangrene of skin of heels and back; osteomyelitis of clavicle; prostatic abscesses with rupture into rectum
115	Trace	4+	...	Sulfathiazole	Bilateral papillary necrosis with cortical abscesses
50	1+	2+	...	.....	Bilateral papillary necrosis with solitary abscess in cortex; femoral thrombophlebitis; cerebral softening
...	0	4+	4+	Retention catheter	Bilateral papillary necrosis; few abscesses in cortex; benign hypertrophy of prostate with obstruction; bronchopneumonia
35	3+	4+	1+	Sulfadiazine	Bilateral papillary necrosis with no abscesses in cortex; carbuncle of skin; lateral sinus thrombosis; pulmonary embolism
...	0	4+	1+	Sulfathiazole	Bilateral papillary necrosis with cortical abscesses; acute pancreatitis; facial hirsutism
87	...	...	...	.....	Bilateral papillary necrosis with thrombosis of renal veins; gangrene of foot
85	...	...	4+	Retention catheter; "urinary antiseptics"	Bilateral papillary necrosis without cortical abscesses; chronic cystitis; severe coronary arteriosclerosis; recent myocardial infarction
75	1+	4+	Rare	.....	Bilateral papillary necrosis with cortical abscesses; acute cystitis; hydrothorax
26	2+	4+	...	Penicillin	Unilateral papillary necrosis with cortical abscesses; bilateral perinephritic abscesses; coronary arteriosclerosis; recent myocardial infarction
112	Trace	4+	...	.....	Bilateral papillary necrosis with 0.5 mm. cortical abscesses; early ulcerative cystitis; mild acute ureteritis; gangrene of toes
to 100	1+	4+	1+	.....	Bilateral papillary necrosis with cortical abscesses; urethral stricture with obstruction; acute cystitis and ureteritis
				Healed Papillary Necrosis	
45	4+	4+	...	Sulfathiazole	Healed lesion of papillae; benign hypertrophy of prostate with obstruction; pulmonary tuberculosis; pulmonary edema; coronary sclerosis
				Granulomatous Lesions with Papillary Necrosis	
...	1+	4+	...	Bladder irrigations; sulfathiazole	Unilateral papillary necrosis; hypertrophy of prostate with acute cystitis; tubercles of spleen
00	1+	4+	1+	.....	Papillary necrosis of remaining kidney with small cortical abscesses; pyoureter and pyonephrosis

many instances the carbon dioxide combining power and nonprotein nitrogen were not determined within one or two days of th.)

§ 4+ means loaded with white blood cells or red blood cells.

A white man of 41 years (10 in table 2) entered the hospital on Nov. 16, 1938, in a semistuporous state. Diabetes had been discovered eleven years previously (1927) and treated for one year with 27 units of regular insulin. Thereafter he took no insulin and followed no diet. He claimed that he had felt well until a few months before entry, when he noted increased thirst and appetite and frequency of urination. Fifteen days prior to hospitalization a "pimple" developed on the back of his neck, which gradually increased in size. Three days before entry it was incised and drained. After this he felt weak, confused and short of breath.

Physical examination revealed an acutely ill, semicomatose man with respiration of the Kussmaul-Kien type and acetone breath. The temperature was 98 F.; the pulse rate, 104; the blood pressure, 100 mm. of mercury systolic and 70 diastolic; the respiratory rate, 22. There was a large carbuncle on the posterior aspect of the neck, with induration extending from the angle of the left jaw to the right posterior aspect of the neck and from the occiput to below the base of the neck. The remainder of the examination disclosed nothing remarkable.

After twenty-four hours of rigorous therapy with insulin and fluids for diabetic acidosis, cautery excision of the carbuncle was done on November 17. Pus was found deep in the neck under the trapezius muscle. As the lesion spread, a more extensive cautery excision (7 inches [18 cm.] in diameter) was performed on November 22. Abscesses appeared on the buttocks and the left ankle, and cellulitis of the left side of the face and left ear developed. The lesions all required surgical incision. Staphylococcus aureus was grown on culture of material from the abscess of the ankle. On December 21 the patient complained of pain in the left upper quadrant of the abdomen, where an indefinite mass was palpated. The bladder was distended at this time, with overflow incontinence, and the urine was loaded with red and white blood cells. He received seven transfusions of 250 cc. each of whole blood. He also received a total of 50,000 units of staphylococcus antitoxin intravenously on December 8 and 9. This treatment was not continued, because of a severe reaction. About 80 Gm. of sulfapyridine was given between December 31 and Jan. 3, 1939. Despite these measures the patient became weaker, pulmonary edema developed and death occurred on January 4, one and a half months after the patient entered the hospital. Throughout the hospital stay the temperature varied between 99 and 101 F. daily. The diabetes was never well controlled, despite the use of 100 to 130 units of insulin daily (regular and protamine zinc insulin). During the last two days of life the blood culture was positive for Staph. aureus. The output of urine remained unchanged throughout. The nonprotein nitrogen level was not determined.

The onset of pyelonephritis as a complication of sepsis was evident in this patient two weeks before death. Sulfapyridine was given for only four days. In retrospect no special clinical symptoms point to the beginning of the papillary necrosis complicating the pyelonephritis.

In group 2 (infection primary in the urinary tract) there were 12 patients.

A 50 year old woman (9 in table 2) entered the hospital on Oct. 4, 1938, with a history of weakness following bronchopneumonia one and a half years previously. She had been told in the year prior to entry that she had diabetes, and was treated with regular (?) insulin—5 to 10 units, one to two times daily—for three months without relief. Later she had been told that she did not have diabetes by a chiropractor who gave her electrotherapy treatments directed to the kidneys. A loss of 51 pounds (23 Kg.) and tingling of the feet had occurred over a period

of one year. Seven days before entry she noted chills, fever, and pain, which was dull and constant, in the left upper quadrant of the abdomen. With this there was urination every two or three hours, accompanied by slight burning. She had had "pink urine" (which she thought to be blood and pus) for one day.

On physical examination this patient was a well developed but emaciated middle-aged woman who appeared weak and chronically ill. The temperature was 98.6 F.; the pulse rate, 96; the respiratory rate, 30; the blood pressure, 84 mm. of mercury systolic and 45 diastolic. The tongue was red, dry and smooth. The heart and the lungs were not remarkable. The abdomen was obese and distended. Tenderness on deep pressure was noted in the left upper quadrant, where an indefinite mass could be felt. There was also tenderness in the left costovertebral angle. The pelvic examination gave essentially normal results.

On October 10 retrograde pyelograms showed a normal right renal pelvis. On the left there was irregular constriction of the renal pelvis and calices, with dilatation of a few minor calices. The superior calices, major and minor, showed generalized constriction and some apparent elongation.

Cystoscopic examination was performed, and ureteral catheters were inserted in the right and left renal pelves to remain for periods of four to nineteen days on five occasions from October 9 to the time of death on December 15. She received two courses of treatment with sulfanilamide, one of three days and one of nineteen days, supposedly 90 grains (5.8 Gm.) a day, but she frequently refused the medicine. The diabetes was easily controlled by diet, with no insulin or with small doses of regular insulin (10 units, two times daily). When she entered the hospital, her temperature was 103.8 F. but dropped to 101 the next day and then became low grade for the next two weeks. On both October 20 and 22 she had a chill, associated with a rise of temperature to 102 F. During the last two or three weeks of life her temperature was normal. In the last week of life she was weak and ate poorly. The volume of urine was not accurately charted but was reduced to 200 to 400 cc. per twenty-four hours during the last few days of life.

The laboratory examination on entry disclosed a leukocyte count of 18,850, with 93 per cent neutrophils, and a nonprotein nitrogen level of 124 mg. per hundred cubic centimeters of blood. With ureteral catheterization the nonprotein nitrogen level dropped to 60 mg. on October 17, only to rise again slowly over the course of two months to a terminal level of 248 mg. Throughout the course of the disease variable amounts of casts, erythrocytes, leukocytes and E. coli were noted in the urine.

Despite the early diagnosis of the pyelonephritis and its vigorous treatment, the patient failed to respond. The roentgen findings on October 10 suggest the onset of papillary necrosis early in the disease, which may explain the poor therapeutic results.

In group 3 (coma due to papillary necrosis) there were 7 patients.

A 63 year old woman (12 in table 2) entered the hospital in deep coma on Jan. 17, 1941 and died two and a half days later. The only history available was that of diabetes of many years' duration. She had not followed a diet well and had taken no insulin. There had been a loss of weight of 40 to 50 pounds (18 to 22.5 Kg.) in a few months. Five days prior to entry she contracted what she termed "influenza," with high fever, loss of appetite and polyuria.

The physical examination revealed a deeply comatose middle-aged woman. Her temperature was 101.6 F. rectally; the pulse rate, 140; the respiratory rate, 40; the blood pressure, 140 mm. of mercury systolic and 110 diastolic to 170 mm.

systolic and 90 diastolic. The heart, the lungs, the abdomen and the pelvic organs were without abnormality.

The urine contained albumin (2+), many pus cells and sugar (4+) but no acetone. The hemoglobin content of the blood was 95 per cent; the erythrocyte count was 4,500,000, and the white blood cell count, 14,800. The carbon dioxide-combining power was 29 volumes per cent on entry and rose to 59 on the second hospital day. The nonprotein nitrogen was 137 mg. per hundred cubic centimeters of blood.

The fulminating course in the presence of coma and evidence of pyelonephritis is characteristic of this group. The rapid course emphasizes the importance of the urinary findings and prompt treatment.

Roentgenologic Findings.—Retrograde pyelograms were taken in 4 cases. In 1 (9 in table 2) the pyelogram of the left side showed an irregular constriction of the renal pelvis and calices, with some dilation

Fig. 1.—The pelvic and calicine systems are well filled. There are two major calices. The minor calices exhibit erosion along the borders of their proximal outline, with a small amount of extravasated dye extending into the cortex of the kidney (patient 13 in table 2).

of a few of the minor ones. There was also general constriction of the superior calices, major and minor, with some apparent elongation. This was considered consistent with pyelonephritis except for the elongation, which suggested renal tumor or abscess. The pyelogram made of the right side on entry was normal. In 1 patient (29 in table 2) the minor calices showed irregularity and destruction. M. B. (7 in table 2) had, as shown by retrograde pyelography, an enlarged right kidney with little opaque medium beyond the region of the ureteral-pelvic junction. The appearance was suggestive of a renal tumor. The urogram of the left side was normal. Figure 1 illustrates the changes in the kidney in the fourth patient (13 in table 2), in which there was erosion of the

minor calices, with a small amount of extravasated dye extending into the cortex of the kidney.

These four studies illustrate the varied types of pyelograms which may be seen, from that of uncomplicated pyelonephritis to that of the ragged, moth-eaten stage of pyramidal necrosis, which has heretofore been associated only with renal tuberculosis. In 2 cases renal tumor was suggested because of renal enlargement or because of distortion of the calicine pattern with elongation.

Pathologic Observations.—Gross Examination: The disease was bilateral in 18 patients and unilateral in 8. In 2 of the latter group the changes were due to hypertrophy of the prostate; in 2 they were

Fig. 2.—Acute necrosis of the renal papillae with extension into the pyramids (patient 14 in table 2). Note that in the uppermost pyramid the necrosis extends almost to an arcuate artery. The renal pelvis is not greatly inflamed. A moderate number of small abscesses are present in the cortex. The reproduction is three-fourths actual size.

secondary to ureteral strictures, and in 1, to a pelvic abscess complicating pyosalpinx. Certain gross features are of interest. The dirty gray–yellow necrotic papillae stood out in striking contrast to the remainder of the renal parenchyma (fig. 2). The shape of the necrotic area was most often that of a segment of a circle, the rounded to flame-shaped base being not far from the limits of the pyramids but rarely reaching the arcuate artery. Thus a major portion of the pyramid might be necrotic. Each radial side of the necrotic area, as a rule, formed a straight line from the papillary-calicine angle and never

encroached on the renal column of Bertin. In less advanced lesions (3 cases) the necrotic areas involved only the tips of the papillae or were centrally located and had an irregular, serrated configuration parallel with the long axes of the collecting tubules. A diffuse involvement of all of the papillae was noted in one or both kidneys in all of the cases in which we made a gross examination. In regard to the older material, in the diagnosis of which we depend principally on microscopic examination alone, this point cannot be settled. The gross appearance of the remainder of the kidney varied greatly. In about a third of the cases no abscesses were seen in the cortex; in a majority (18 cases) abscesses measuring 1 to 2 cm. in diameter were present. Widespread necrosis of the cortex was seen only once.

In patients with sepsis secondary to a focus other than one in the urinary tract producing descending pyelonephritis, the pelvis and calices were only mildly hyperemic. Even with ascending infections the degree

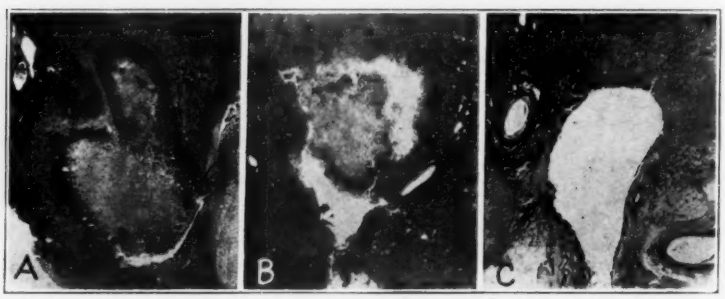


Fig. 3.—Three stages of papillary necrosis. *A*, acute necrosis (patient 22 in table 2); × 4. *B*, sequestration of papillae (patient 22 in table 2); × 4. *C*, papillae eliminated (patient 2 in table 2); × 4.

of pyelitis seemed grossly out of proportion when compared with the degree of necrosis of the papillae (Günther [1] emphasized this point) except in 2 instances in which there was ureteral obstruction. Severe cystitis was noted only once. Thus the gross findings in one group suggested that what began as a mild, relatively symptomless infection of the lower urinary tract suddenly was converted into a highly fatal disease when it reached the papillae.

Microscopic Examination: Necrosis of the papillae was complete except in the 3 cases mentioned in a foregoing paragraph. In addition, from two thirds to three fourths of the pyramids were likewise involved, usually to a uniform depth, but occasionally the margin of the necrotic zone was irregular. In nearly all of the group the necrotic process had apparently advanced to about the same stage when death occurred. However, in the kidney of one patient (3, table 2) sequestration had

begun, and in that of another (26, table 2) many of the papillae had been cast off, even though other papillae were still attached. The three stages which may occur—i. e., necrosis, sequestration and elimination —are illustrated together (fig. 3). Within the areas of necrosis an

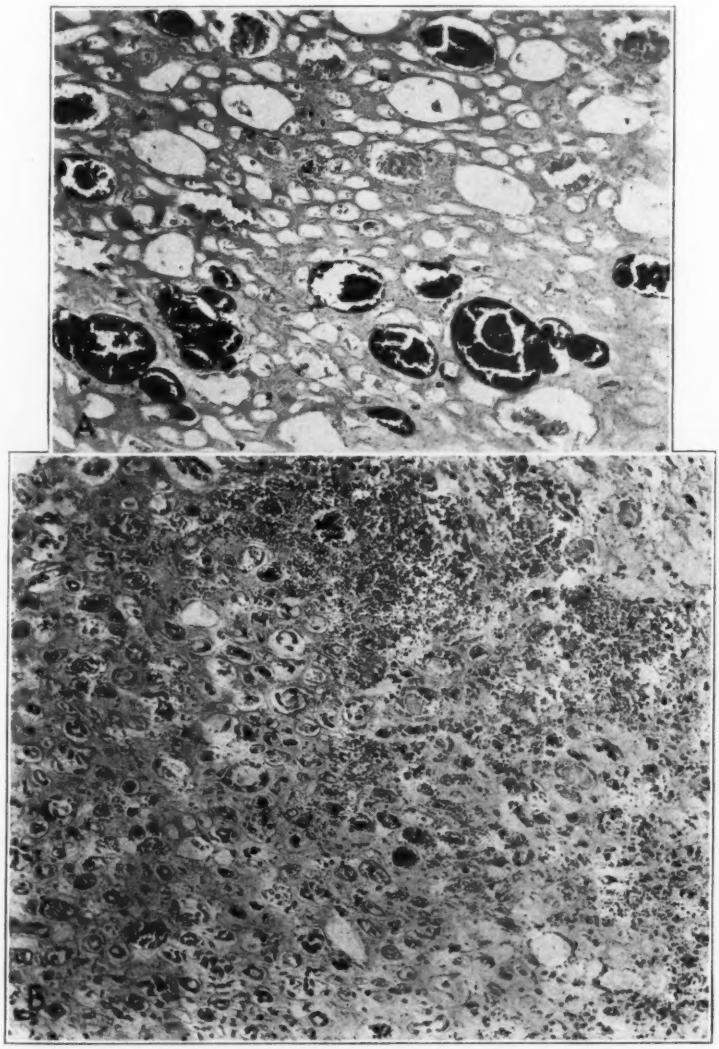


Fig. 4.—*A*, necrotic tubules filled with dark masses of organisms (patient 23 in table 2); × 150. *B*, absence of interstitial cellular exudate at margin of necrotic zone (patient 22 in table 2); × 185.

outstanding feature of the lesions caused by staphylococci was the tubules filled with blue-staining organisms (fig. 4 *A*), described by Günther.[1] The base of the necrotic area, with one exception, was

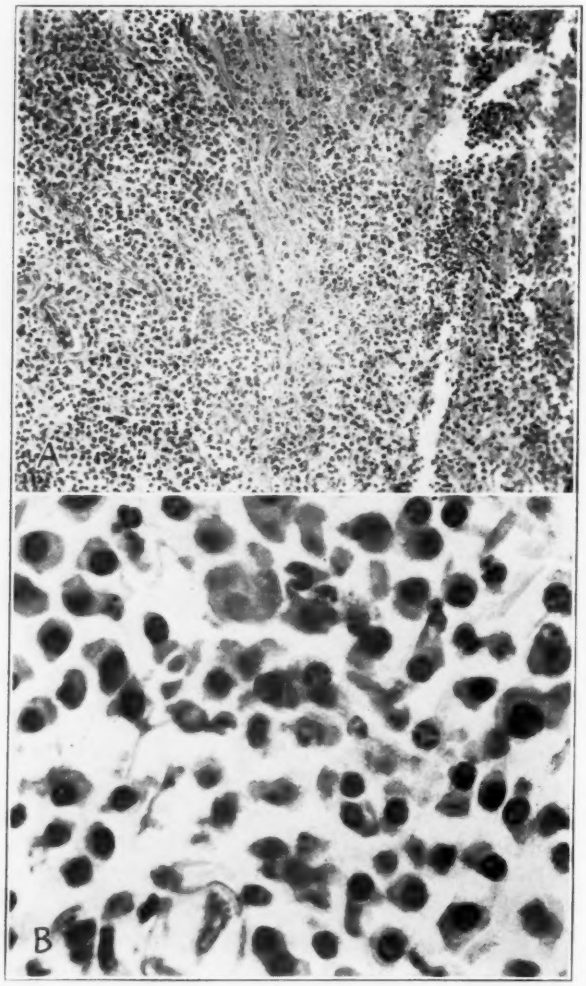


Fig. 5.—Area at margin of a necrotic zone infiltrated with plasma cells and other mononuclears (patient 23 in table 2). *A*, × 105. *B*, × 385.

within the pyramid, and no glomeruli were included. The inflammatory reaction at the junction of necrotic and surrounding tissue was of particular note. In some places not a single inflammatory cell could

be seen in the intercellular spaces (fig. 4*B*). Apparently the toxic action of the bacteria was lysing tissue unopposed by any protective action on the part of the body. In other areas neutrophils, eosinophils, plasma cells and lymphocytes formed an inflammatory zone of variable thickness. The plasma cells were numerically greater than or equal to the other inflammatory cells in about half the kidneys (fig. 5), though this varied greatly, even in the same pyramid. They usually formed a secondary line of defense just back of the line of scrimmage between the necrotizing process and the viable tissue. The dearth of neutrophils was especially noticeable (fig. 5) for such an acute necrotizing lesion. The collecting tubules near the necrotic zone often contained polymorphonuclear leukocytes and bacteria, but usually a majority were

Fig. 6.—Hyaline thrombus in a small vessel near the margin of a necrotic zone (patient 21 in table 2); × 110.

free of exudate. Thrombosis of capillaries, usually hyaline, was seen within a narrow zone of the intact parenchyma in a few kidneys (fig. 6). In 5 kidneys extensive thrombophlebitis of the venous system was noted.

In the ascending type of infection the organisms evidently spread to the cortex via the tubules, many of which were seen to be filled with bacteria, neutrophils and necrotic debris. In 8 of the group this was the only infectious process in the cortex. In the more severe lesions (16 cases) localized abscesses had formed, involving many tubules. They were usually 1 to 2 mm. in diameter, few, and adjacent to the bases of the pyramids. In a few lesions the abscesses were 0.5 to 1 cm. in size. In 2 kidneys solitary abscesses were the only change seen in the cortex. Again it was observed that the inflammatory response was

characterized by a relative paucity of neutrophils but many plasma cells. An unusual degree of necrosis was seen in the abscesses with karyolysis, similar to that noted in the papillae, in 3 cases.

The effect of the necrosis of the conduits on the outflow of urine in the nephrons is a problem in itself. In only 9 cases was there any evidence of obstruction causing dilatation such as that seen in the obstructive nephroses due to sulfonamide drugs and hemoglobin. This coincides with the clinical records of a normal urinary output in nearly all cases. Further and more complete investigation of this phase of the disease is needed.

Changes were present in the renal arterial tree without exception. The most noticeable was the intercapillary deposition of hyalin as described in Kimmelstiel-Wilson disease. Mild to moderate hyaline change was seen in 12 of the 26 cases (fig. 7 *A*). Severe damage was noted in 3, resulting in many hyalinized, functionless glomeruli. Sclerosis of the arteries and arterioles was mild in 17 and severe in 9 (fig. 7 *B*).

In sections of the pelvis and calices a moderate degree of acute to chronic inflammation was seen. The cellular picture was often similar to that in the interstitial tissue of the kidney. In 3 instances the round cell infiltration without polymorphonuclear cells noted in the pelvis, the cortex and the capsule of the kidney was of sufficient intensity to justify a diagnosis of chronic pyelonephritis, although scars with colloid casts and periglomerular fibrosis as described by Weiss and Parker [16] were not present.

HEALED PAPILLARY NECROSIS

There was one diabetic patient (27 in table 2) in whom the renal papillae had undergone partial to complete necrosis and sloughed away, leaving the base apparently well healed.

The patient, an 81 year old white man, entered the hospital because of exertional dyspnea. He had had frequency of urination for one year but had not known that he had diabetes. On examination the prostate was soft and enlarged to twice the normal size. The blood pressure was 105 mm. of mercury systolic and 60 diastolic. The urine on entry contained no protein and only 3 to 4 pus cells per high power field. The electrocardiogram revealed low voltage and delayed auriculoventricular conduction. Following a fall, an ulcer developed on the ankle, which became infected. He then began to vomit. After several weeks albuminuria (albumin, 4 plus) and severe pyuria were observed. General edema developed. The serum albumin was 3.2 Gm. and the nonprotein nitrogen was constantly between 43 and 52 mg. per hundred cubic centimeters of blood. He died three and a half months after entry.

The cause of death was attributed to acute pulmonary edema due to hypoproteinemia caused by proteinuria and poor food intake. The

16. Weiss, S., and Parker, F., Jr.: Pyelonephritis: Its Relation to Vascular Lesions and to Arterial Hypertension, Medicine **18**:221, 1939.

papillary necrosis of the kidneys apparently did not contribute to the cause of death. Grossly the process was unilateral and partial. On microscopic examination the absent portions of the papillae comprised

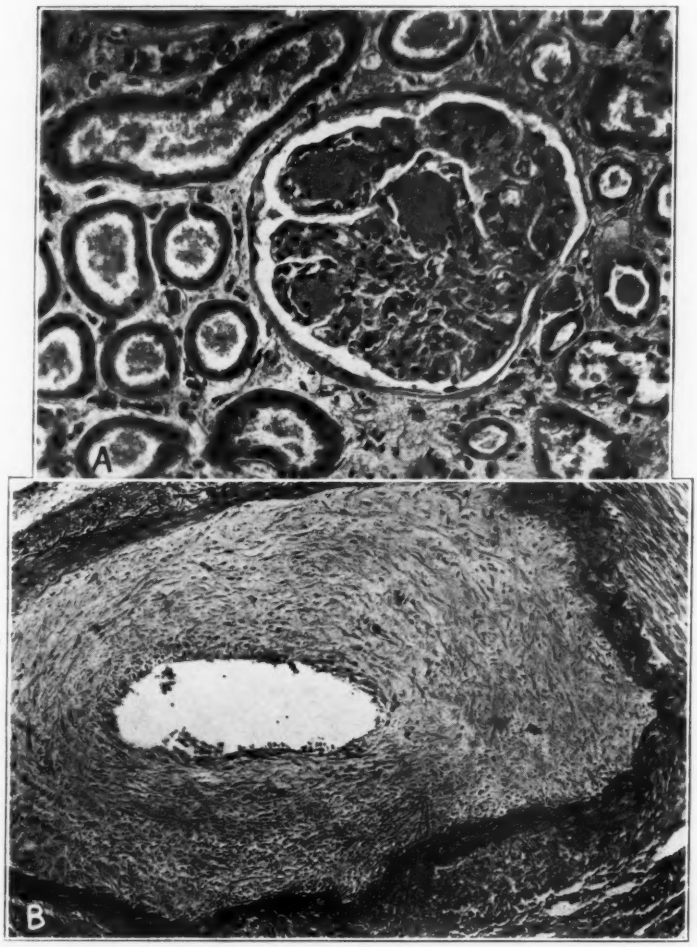


Fig. 7.—*A*, intercapillary glomerulosclerosis of moderate severity (patient 21 in table 2); × 250. *B*, severe sclerosis of larger interlobar branch of renal artery (patient 20 in table 2); × 90.

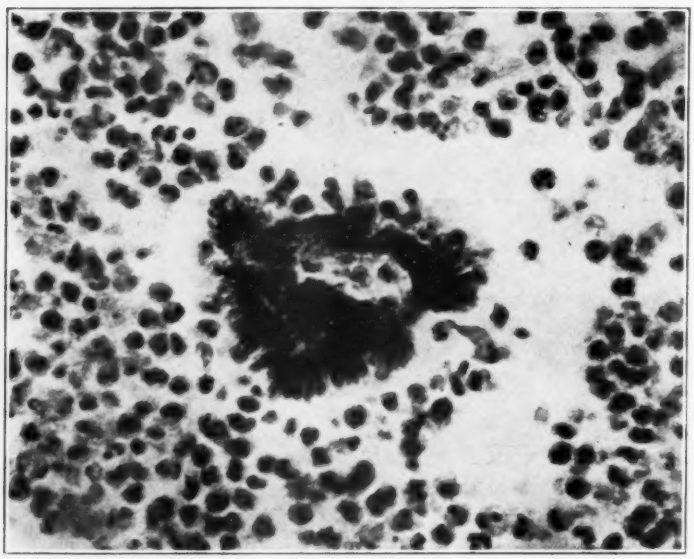
less than one half of the total. Many of the remaining collecting tubules were hyalinized and functionless, although connective tissue proliferation was slight. Some fibrin, a few polymorphonuclear leukocytes and

mononuclear cells were noted between the tubules. No inflammatory changes were visible in the cortex. Some of the papillae were unaffected.

PAPILLARY NECROSIS DUE TO GRANULOMAS IN DIABETIC PATIENTS

Of particular interest were 2 diabetic patients in whom typical necrotizing lesions were apparently granulomatous in origin.

In the case of 1 of these (28 in table 2) with unilateral involvement the microscopic picture was difficult to interpret. The necrotic areas were similar to the others except for the fact that throughout they were more basophilic and at



No. 8.—Sulfur granule of actinomycosis (patient 29 in table 2): × 350.

their margins there were occasional epithelioid cells. Smaller but more characteristic tubercles were noted in other parts of the pyramid; none were seen in the cortex. In a section prepared with the Gram-Weigert stain occasional gram-positive cocci were seen in the tubules. Acid-fast organisms were not observed, however, in a prolonged search. Since miliary tubercles were present in the spleen, a diagnosis of tuberculosis combined with pyogenic invasion seemed tenable. There was nothing distinctive in the patient's clinical history. Apparently the course was similar to that of other patients in whom the disease was caused by pyogenic organisms only.

The second patient (29 in table 2) was a 59 year old woman who entered the hospital with a history of pain in the right upper quadrant of the abdomen, cough and vomiting of two months' duration. There had been a 50 pound (22.5 Kg.) loss of weight in two years. On physical examination a mass was found in the right

upper region of the abdomen, which was considered to be the right kidney. The urine contained pus (4 plus), sugar and acetone. Antemortem culture of the urine from the right kidney was negative for acid-fast organisms. Retrograde pyelography gave a normal left ureteropyelogram. On the right the minor calices, particularly the upper, appeared distorted and irregular. After right nephrectomy the patient's illness continued to follow a stormy course. A draining sinus developed in the operative wound. Pus appeared in the urine of the left kidney, the nonprotein nitrogen rose to 109 mg. per hundred cubic centimeters of blood and the patient died within two months in uremia. There was nothing in the clinical history that suggested a gramulomatous lesion.

Microscopic examination of the kidney removed at necropsy showed large areas of shadow-like necrosis which had at their margins in the bases of the pyramids and along the renal columns typical pus-filled cavities containing many of the organized filaments (sulfur granules) of actinomycosis (fig. 8). In the inflammatory exudate polymorphonuclear leukocytes were in great numerical predominance. The available sections of the kidney removed in surgical intervention were made by the frozen method, and the contents of the cavities had fallen out; so no organisms were seen. The histologic picture was that of a granuloma. The papillae were not necrotic. No other lesions of actinomycosis were observed in the body.

ACUTE PYELONEPHRITIS WITHOUT PAPILLARY NECROSIS IN DIABETIC PATIENTS

In this group there were 78 patients, 9 per cent of the patients with diabetes. In 28, or 35.8 per cent, of them the pyelonephritis was due to infection arising elsewhere than in the urinary tract. In 9, no cause

TABLE 3.—*Analysis of Clinical Factors in the Twenty-Nine Patients*

Sex	65% females		
Age	79% over 50		
Cause of entry	Urinary symptoms	20.5%	41%
	Uremia	20.5%	
	Diabetic acidosis	17%	
	Cutaneous infections	14%	(31% if those in whom severe cutaneous infections developed on ward are included)
	Miscellaneous	28%	
Hypertension	24%		
Duration of hospitalization before death	62% less than 15 days 38% over 1 month (1 to 10 months)		

of the acute pyelonephritis was apparent in the lower urinary tract, nor was a focus of infection noted elsewhere. In the remainder the pyelonephritis was a complication of infection and/or obstruction of the urinary tract. There were 38 women and 40 men.

In a comparison of these patients and diabetic patients having papillary necrosis there are some data of interest. There was little difference in average age incidence. There were 6 patients, however, under the age of 40 with uncomplicated pyelonephritis, contrasted with only 1 patient under the age of 40 with papillary necrosis. There was

a higher percentage of women with the necrotizing lesion (65 per cent, compared with 49 per cent who had pyelonephritis alone). Obstructive lesions of the urinary tract were more common in the group with pyelonephritis alone (occurring in 26 per cent, compared with 14 per cent of the group with papillary necrosis). Fewer of this group had coma before the apparent onset of the acute disease of the kidney or died in coma as a complication of the latter.

Grossly the kidneys were similar to those of nondiabetic patients with suppurative renal disease. A few had solitary abscesses and perinephric abscesses. On histologic examination this group on the average differed from those with papillary necrosis in that cortical abscesses were more common, neutrophils were more prevalent, and the extent of necrosis

No. 9.—Early necrosis of a solitary collecting tubule in beginning pyelonephritis; × 150.

was not so much out of proportion as compared with the total inflamed area. In this group there was every gradation in the necrotic process from pus-filled abscesses mainly in the cortex to diffuse multiple necrotizing lesions (8 cases) in both the cortex and the pyramids, differing from papillary necrosis only in that the necrotic areas in the papilla were small (fig. 7 *A*) and involved only a minor portion of the total papilla and pyramid. Thrombosis of veins such as that seen by Harrison and Bailey [15] was noted in 4 cases. Other differences included a smaller number with Kimmelstiel-Wilson lesions (18.5 per cent) and less severe sclerosis of the arterial system. An attempt was made to compare the proportion of the various cells of the renal exudate with that in the group with papillary necrosis. The predominating cells were either neutrophils or lymphocytes, but abundance of plasma cells

was a fairly constant finding. The latter were never so outstanding as in some instances of papillary necrosis, in which the plasma cells constituted the major portion of the cellular exudate (fig. 5). Obviously this comparison was a difficult one to make because of the lack of a good measuring stick, but we feel that the foregoing opinion is justified.

PAPILLARY NECROSIS IN NONDIABETIC PATIENTS

Among the 31,141 nondiabetic subjects there were 1,023 with a diagnosis of pyelonephritis or pyonephrosis. Of these, 21 had either bilateral or unilateral necrosis of the papillae. Table 4 gives the essential data. It is seen that prostatic lesions are the most important cause

TABLE 4.—*Papillary Necrosis in Nondiabetic Patients*

Patient	Primary Disease	Gross Pathologic Condition of Urinary Tract	Age	Sex	Papillary Necrosis
1	Benign hypertrophy of prostate	Infected obstructive uropathy	65	M	Bilateral ?
2	Benign hypertrophy of prostate	Infected obstructive uropathy	87	M	Bilateral
3	Benign hypertrophy of prostate	Infected obstructive uropathy	77	M	Unilateral
4	Benign hypertrophy of prostate	Infected obstructive uropathy	80	M	Unilateral
5	Benign hypertrophy of prostate	Infected obstructive uropathy	78	M	Unilateral
6	Benign hypertrophy of prostate	Infected obstructive uropathy	80	M	?
7	Benign hypertrophy of prostate	Infected obstructive uropathy	80	M	?
8	Carcinoma of prostate	Infected obstructive uropathy	62	M	Unilateral
9	Carcinoma of prostate with postoperative stricture	Infected obstructive uropathy	55	M	?
10	Carcinoma of prostate	Infected obstructive uropathy	74	M	Unilateral
11	Carcinoma of prostate	Infected obstructive uropathy	74	M	Bilateral
12	Carcinoma of bladder	Unilateral pyonephrosis	65	M	Unilateral
13	Carcinoma of bladder	Bilateral pyonephrosis	53	M	Unilateral
14	Carcinoma of cervix	Bilateral pyonephrosis	61	F	Bilateral
15	Carcinoma of cervix	Unilateral pyonephrosis	30	F	Unilateral
16	Urethral stricture	Necrotizing obstructive uropathy	45	M	Bilateral ?
17	Urethral stricture	Bilateral pyonephrosis	44	M	Bilateral
18	Bilateral renal calculi	Bilateral pyelonephritis	58	M	Unilateral
19	Postvaccinal paraplegia with "cord bladder"	Infected obstructive uropathy	11	F	Bilateral
20	Hypertensive heart disease with congestive failure	Only peculiar appearance of pyramids noticed grossly	51	M	Bilateral ?
21	Adenocarcinoma of ovary with spread to bladder	Bilateral pyelonephritis with abscesses in left kidney	33	F	Unilateral ?

in the nondiabetic patients. In 20 of the 21 there was chronic obstruction of the urinary tract. The incidence of necrosis in this group has definitely decreased in recent years, presumably owing to better control of infections of the urinary tract with sulfonamide drugs and penicillin.

Pathologic Observations.—The gross necrotic lesions were rarely described by the autopsy surgeon. They were probably overlooked because of the overshadowing effect of the primary disease of the urinary tract, in contradistinction to the lesions of the papillae in diabetic patients, which usually stand alone as gross pillars of pathologic change. The histologic picture differed from that of the diabetic group in that the lesion was usually smaller and more often confined to the tip of the papilla or was present only in its central portion. Plasma cells were rarely outstanding in the cellular exudate. Again, as in the diabetic

group, all gradations were seen between microscopic abscesses in the papillae and extensive necrosis. Thrombosis of renal vessels did not appear to be a factor.

Clinical Findings.—A review of the clinical records of these patients gave no clues to how an antemortem diagnosis could be made. As Günther [1] pointed out, the primary disease plus infection usually completely masks the necrosis in the kidneys.

COMMENT

The major clinical problems connected with papillary necrosis concern diagnostic criteria, differential diagnosis and treatment. No clinical diagnosis of Günther's necrosis that was substantiated by autopsy was made until after this study was begun. The condition has now been diagnosed ante mortem in several patients. We do not believe that rigid diagnostic criteria can be laid down for all cases. However, the lesion should be considered in any investigation of the following types of diabetic patients: (1) those with sepsis in whom urinary symptoms or findings suddenly develop, (2) those who go into coma rapidly with nitrogen retention but without an antecedent history of pyelonephritis, (3) those with low grade pyelonephritis who suddenly become worse, (4) those with hematuria or renal colic, (5) those with severe diabetic acidosis whose blood sugar and carbon dioxide–combining power may return to normal after treatment but who show an increasing degree of stupor and rising nonprotein nitrogen when shock and tubular damage can be excluded, and (6) those with characteristic roentgenographic changes.

In many cases the pyelograms are diagnostic, particularly if the lesions are bilateral and symmetric. All gradations of involvement of the papillae may occur; hence the appearance of the calices on roentgenograms depends on the degree of necrosis. Günther [1] and Alken [11] emphasized the following roentgenographic changes: (1) The earliest lesion is a deformity of the tip of the calix such as that seen in pyelonephritis; (2) with narrowing of the neck of the calix by separated particles, a picture of peripheral excavation extending into the cortex may occur; (3) ring shadows may be seen in the necrotic papillae; (4) replacement of the concave tip of the calix by dilation so great as to suggest cavern formation; (5) tips of whole papillae may slough off and appear as free masses in the renal pelvis.

In the differential diagnosis the diseases to be considered are: (1) pyelonephritis without necrosis, (2) stone with renal colic, (3) renal tuberculosis and (4) renal tumor. When pyelonephritis is present without necrosis, the patient is rarely as ill and the course is less fulminating than when necrosis is present. Pyelograms may be diagnostic in some cases but will not be so in all, since the differences between the

two groups are not always marked or striking. Stone with symptoms of renal colic may be confused with Günther's necrosis when colic is caused by sloughing-off of a necrotic papillary tip and resulting ureteral blockage. The pyelogram may or may not be helpful here, for stones and sloughed tissue may be roentgenographically similar. The diabetic state and the course of the disease may favor the diagnosis of the necrotic lesion. In some cases surgical intervention alone may establish the diagnosis (illustrated in the case of Mellgren and Redell [12]). We have had no patients who presented renal colic. We are aware of a patient of a confrere, whose renal necrosis was diagnosed by roentgenograms and study of the kidney and who was treated by surgical removal of the kidney, whose presenting symptom was severe renal colic. This patient is alive after one year.

In diabetic patients with hematuria, all the usual causes should be excluded. With renal tuberculosis or tumor this may be difficult, for the pyelographic outline may be similar to that seen in necrosis. However, in most diabetic patients both kidneys and all of the papillae become involved, which should be diagnostic. In unilateral disease differential points are few or absent. Recently we have observed an elderly diabetic patient who died four days after she first entered the hospital with symptoms of high fever, cardiovascular disturbances, pyuria and hematuria, who was too ill for pyelograms to be made. We diagnosed papilary necrosis, but a hypernephroma was found at necropsy.

In a consideration of the cause or causes of this unusual necrotizing lesion, several factors may be considered. First, as Günther [1] and others have emphasized, is the anatomic fact that the papillae and the pyramids have a poor blood supply as compared with the rest of the kidney. All of the blood except a small amount from branches of the arteries that directly supply the renal pelvis reaches the peritubular capillaries after it has gone through the glomeruli. In addition we would emphasize the physiologic fact that the blood has now lost 10 per cent of its water, much of its sugar, chlorides and nitrogenous products while retaining its protein, and thus its osmotic pressure is increased. Whether or not this may have an effect on the migration of leukocytes is not known, but presumably such blood, being more viscid, tends to undergo intravascular clotting more readily. The fact that the necrosis is anatomically limited to the pyramids is in itself strong evidence of the importance of the blood supply. At least no other explanation for its abrupt limitation at the arcuate vessels and the papillary-calicine angle comes to mind. Contributing further to the lack of blood flow are the sclerotic changes in the arterial system. These were present in all kidneys. The arterial and arteriolar changes were mild to moderate in 17, while in the remainder the changes were severe. Intercapillary glomerulosclerosis, seen in 60 per cent, would further tend to embarrass

the pyramidal blood flow. In patients with severe Kimmelstiel-Wilson disease, in whom loss of protein was sufficient to produce hypoproteinemia, the effect on immune processes, especially the possible decrease of gamma globulin, is one to be considered and one well worth further investigation.

Second, and possibly more important, is the diabetic state, especially if acidosis is present. Menkin's [17] work on inflammation indicates that in the early stages of the inflammatory process the fluid exudate is alkaline and therefore favorable to the preservation and the function of polymorphonuclear leukocytes. Later, with death of tissue, acid bodies accumulate locally, and as the p_H falls below 6.9 the neutrophils disappear and mononuclears become numerically predominant. Menkin showed that in diabetes acid bodies were formed more rapidly and thus influenced the course of the inflammatory process by causing a more rapid disappearance of polymorphonuclear cells. It seemed to us that the pattern of the cellular exudate in diabetic patients was different from that in nondiabetic patients. Especially in papillary necrosis the exudate was poor in polymorphonuclears. Furthermore, in diabetic acidosis with papillary necrosis, once the basement membrane is necrotic, the effect of a bacteria-laden, highly acid, sugar-filled urine escaping into the intercellular tissues is to be considered. This may effect change in the inflammatory reaction of the tissues in the precise manner already noted; i. e., an exudate small in amount and poor in neutrophils and fibrin accumulates, resulting in an apparent inability to wall off the infection. In obstructive lesions of the urinary tract urine may escape into the tissues through necrotic walls. If there is a normally functioning lower urinary tract, the pressure differential between intercellular fluid and intratubular flow should not be great enough to cause the same phenomenon unless some of the individual tubules are blocked by exudate. Thus the effect may be compared with that seen in urinary extravasation around the urethra, where necrosis of tissue followed by gangrene is common.

The relation of glycosuria to the development of both pyelonephritis and the necrotizing lesion is a problem in itself. An attempt was made to reproduce the lesion in depancreatized rats by prolonged glycosuria and ureteral obstruction (ureters tied with silk). Pyonephrosis developed in all these rats, although depancreatized rats are relatively resistant to infection, whereas only hydronephrosis developed in the nondiabetic rats similarly treated. In none of the rats of either group, however, did the classic Günther's lesion develop. This may have been

17. Menkin, V.: Diabetes and Inflammation, Science **93**:456, 1941; On Mechanism of Enhanced Diabetes with Inflammation, Am. J. Physiol. **134**:517, 1941; Biochemical Factors in Inflammation and Diabetes Mellitus, Arch. Path. **34**:182 (July) 1942.

due to the fact that atrophy was extreme, and by the time the rats died only a shell of pyonephrotic kidney was left. The relationship of hyperglycemia to infection in general and of glycosuria to renal infection in diabetes still remains an unsolved problem despite much experimental work on the subject. The fact that papillary necrosis has been produced by administration of vinylamine [18] and tetrahydroquinone [19] may have some significance in that it indicates the papillae are the parts of the kidney most susceptible to injury by these agents.

A third factor to be considered is the type and the virulence of the bacteria. Early in our studies we assumed that E. coli was the chief offender, but as bacteriologic data accumulated, our attention turned to Staph. aureus. The masses of blue-staining organisms seen in sections of the kidney stained with hematoxylin and eosin are probably staphylococci. In those patients with foci of infection elsewhere, as manifested in carbuncles and cellulitis, on whom no bacteriologic study was made at necropsy we assume that Staph. aureus was the cause of the renal necrosis. In those cases without a distant focus it seems probable that an ascending staphylococcic infection was present. The poor resistance of diabetic patients to Staph. aureus is well known, as carbuncles, cellulitis and infected feet are common complications. The coagulase enzyme (destroying fibrin) of the staphylococcus plus the necrosin factor discovered by Menkin [20] (a euglobulin found in inflammatory exudates, capable of causing necrosis), operating together, help to account for the extensive necrosis seen. Günther [1] noted the presence of E. coli and staphylococci in many of his cases and believed that they were the primary causes of the disease. Baldwin and Root [21] stressed the serious nature of renal infections in the diabetic patient, particularly those of hematogenous origin caused by hemolytic Staph. aureus.

The presence of tuberculosis of an unusual character, apparently combined with a minor degree of pyogenic infection, resulting in papillary necrosis, as it did in one instance in our series, must be extremely rare. Papillary necrosis due to actinomycosis of the kidney is likewise most unusual. The localization of the actinomycotic process in the pyramid in such a way as to produce necrosis of the papilla without directly involving it is difficult to explain. Stoudensky [4] noted both actino-

18. Levaditi, C.: Recherches expérimentales sur la nécrose de la papille rénale, Arch. internat. de pharmacodyn. et de thérap. **8**:45, 1901.

19. Rehns, J.: D'une nécrose typique de la papille rénale determinée par la tétrahydroquinoléine et certains de ses dérivés, Arch. internat. de pharmacodyn. et de thérap. **8**:199, 1901.

20. Menkin, V.: Chemical Basis of Injury in Inflammation, Arch. Path. **36**:269 (Sept.) 1943.

21. Baldwin, A. D., and Root, H. F.: Infections of the Upper Urinary Tract in the Diabetic Patient, New England J. Med. **223**:244, 1940.

mycosis and tuberculosis associated with the disease, but neither caused the papillary lesions.

Other considerations include the known fact that antibody response is poor in many diabetic persons.

No explanation has been presented so far as we know for the excessive plasma cell infiltration evidenced in the inflammatory exudate. This is not a pathognomonic sign, for occasionally similar numbers are seen in nondiabetic patients with pyelonephritis. Mellgren and Redell [12] mentioned plasma cells in their report of papillary necrosis occurring in 2 nondiabetic patients. But if the average over-all histologic picture is taken, the difference in cellular exudates is unquestionable.

The role of the peritubular hyaline substance called para-amyloid by Mellgren and Redell [12] is difficult to evaluate. In our experience an increase of hyaline material around the tubules in the papillae and the medulla is not uncommon in the older age groups. We did not see any increased incidence in the diabetic group.

The spreading type of necrosis observed in the papillae and pyramids, associated with many bacteria and little inflammatory reaction, is really a gangrenous process in the true sense of the word. The formation of a line of demarcation in the pyramid, sloughing of the affected part and finally occasional healing of the pyramidal remnant are further characteristics of gangrene. It differs from gangrene ordinarily seen elsewhere in its precise limitation to multiple small areas. Gangrene as a complication of diabetes is too well known for comment, whether it occurs in the extremities, the skin, the lungs or elsewhere.

The fact that papillary necrosis may occur in diabetic patients without obstruction of the urinary tract, while on the contrary it is practically limited to patients with urinary obstruction in the nondiabetic group, emphasizes the importance of infection in the diabetic group. Of the 107 patients with diabetes, 33.6 per cent had sepsis resulting in secondary renal infection. Better and earlier use of the new chemotherapeutic agents should be helpful in preventing many of these lesions.

The predilection of papillary necrosis for diabetic persons beyond the age of 40 (the condition developed in only 1 of 9 under 40) may be due in part to the severity of vascular lesions occurring beyond that age. No conceivable explanation can be given for the apparently greater incidence of necrosis in women.

Prevention, as already noted, is the most important part of treatment. The use of penicillin and sulfonamide compounds for the staphylococcic infections and possibly in the future the use of streptomycin for E. coli infections may save some of these patients. We have in our series a patient whose lesions healed and know of another (case to be reported). In none of the cases summarized in this article can it be considered that the patient received adequate chemotherapy. In some patients

death occurred too soon after they entered the hospital, and the gangrenous process was too overwhelming by the time the patient was seen, for any form of therapy to be of value. It is essential that urologists realize that the lesions are usually bilateral in those diabetic patients who are without unilateral obstruction, as removal of one kidney with necrosis may speed a latent or an early process in the opposite kidney. In the nondiabetic group the important objective is the treatment of all obstructive lesions.

SUMMARY AND CONCLUSIONS

Acute necrosis of the renal papillae was observed in 29 of 859 diabetic subjects in a series of 32,000 necropsies. Papillary necrosis is more common in women and is exceedingly rare in patients under 40 years of age as contrasted with pyelonephritis without necrosis in diabetic patients, among whom men predominate and occurrence under 40 is not unusual. The disease is highly fatal; only once was healing observed. It is most often part of acute pyelonephritis, which may be secondary to ascending infection of the urinary tract or to pyogenic foci elsewhere in the diabetic subject. E. coli and Staph. aureus are the organisms most frequently isolated from acute pyelonephritis. The latter disease may be secondary to sepsis, which is an important cause of pyelonephritis in diabetic patients. Tuberculosis and actinomycosis were each noted once as the cause of papillary necrosis. The diabetic state, renal vascular disease (including Kimmelstiel-Wilson disease) and poor blood supply of the papillae are apparently contributing factors in the pathogenesis.

In the same necropsy series, papillary necrosis was noted in 21 of 1,023 patients with pyelonephritis who were not diabetic; in 20 it occurred as a complication of urinary obstruction, which was most often due to disease of the prostate gland.

Criteria for the diagnosis of papillary necrosis in diabetic patients cannot be rigidly defined but should include hematuria, renal colic, unexplained coma and sudden increase in severity of symptoms of known pyelonephritis. Retrograde pyelograms are usually diagnostic. Treatment should be directed toward preventing infection by early use of chemotherapy. After the onset of pyelonephritis, specific chemotherapeutic agents should be used in adequate amounts, as some patients may be saved.

EOSINOPHILIC GRANULOMA OF BONE

Report of a Case with Multiple Lesions of Bone and Pulmonary Infiltration

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DURING the past years, approximately 30 cases of eosinophilic granuloma of bone have been reported in the medical literature. Since it has been noted that this condition is confined to the skeleton, often involving only a single bone, it has also been called "solitary granuloma of bone."[1] The case herein reported has been under observation for almost three years since the diagnosis was established and is considered noteworthy because of the presence of multiple skeletal lesions and a coexistent pulmonary infiltration. The latter may well be an instance of visceral involvement.

REPORT OF A CASE

The patient was a 31 year old lawyer who was admitted to the Medical Service of Vanderbilt University Hospital on Jan. 6, 1943, complaining of an intermittent headache in the left occipital region, of about seven months' duration, and backache in the lower region, which he had first noticed three months before his admission.

The headache had begun insidiously and was never severe. It remained localized in the region of the left side of the occiput and was neither constant nor progressive. Remissions for as long as a week were frequent. Use of salicylates usually afforded prompt relief. The headache was not associated with visual disturbances, weakness, paresthesias, syncopal attacks or convulsive seizures.

The only other complaint was that of intermittent ache low in the back, which he referred to the region of the left sacroiliac joint. This pain was aggravated by sudden movement. There had been no apparent limitation of motion and no radiation of the pain into the lower extremity. There was no significant history of trauma. He had been troubled for the past few months by a nonproductive cough. There had been no pains in the chest.

Physical Examination.—At the time of admission, it was noted that he was a robust young man who did not seem ill. His temperature was 98.6 F., pulse rate 110, respiratory rate 22 and blood pressure 122 mm. of mercury systolic

From the departments of medicine and radiology, Vanderbilt University School of Medicine.

1. Otani, S., and Ehrlich, J. C.: Solitary Granuloma of Bone Simulating Primary Neoplasm, Am. J. Path. **16**:479-490 (July) 1940.

and 88 diastolic. Tenderness was observed on deep palpation over an area of 1 to 2 cm. in diameter in the left parietal region of the skull. There was no palpable bony defect or tumor at this site. No intracranial bruit was heard.

Fig. 1.—Roentgenogram of the skull, December 1942, showing defects in the left parietal and the occipital bone.

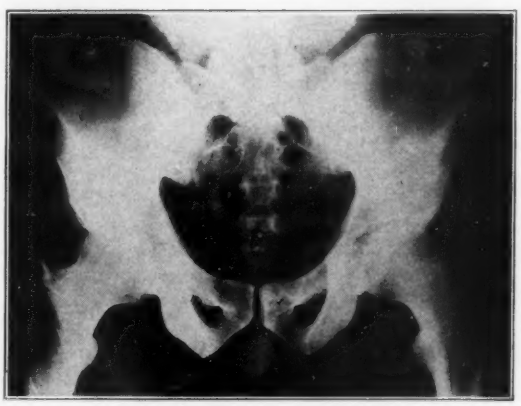

Fig. 2.—Roentgenogram of the pelvis, April 1943, showing destructive area in the left iliac wing and the pubic bones. Gas shadows are present over the right ilium.

Fig. 3.—Roentgenogram taken in March 1943, showing destructive lesion in the third lumbar vertebra.

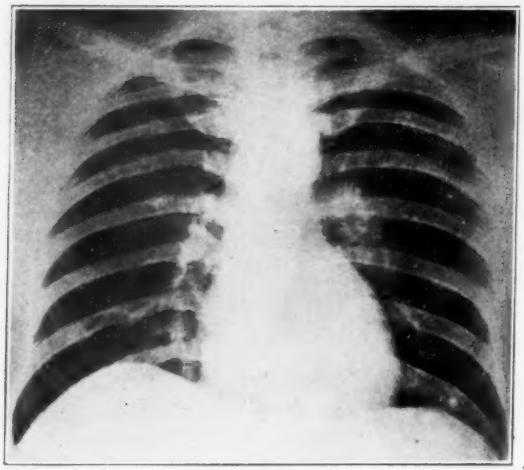

Fig. 4.—Roentgenogram of the chest, March 1943, showing nodular infiltration of the upper fields of both lungs.

The ocular fundi were normal. The thyroid was not enlarged, and there was no enlargement of peripheral lymph nodes. The heart and abdomen were not remarkable. The examination of the lungs revealed no dulness, alteration in breath sounds or rales. There was no demonstrable enlargement of the liver or spleen. Examination of the spine revealed no localized deformity or tenderness, and

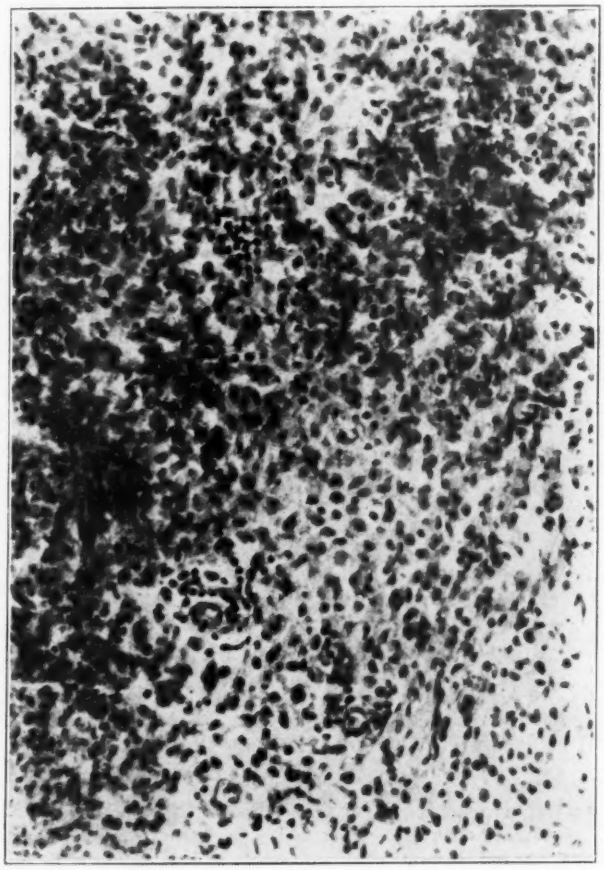

Fig. 5.—Photomicrograph of tumor tissue, showing the large collection of eosinophils and histiocytes.

moblity was unimpaired. The prostate was normal in consistency and size. The cranial nerves were intact. There were no changes in the motor or sensory nerves. The reflexes were physiologic.

Laboratory Studies.—The spinal fluid, which was under normal pressure, contained 3 cells and 36 mg. of protein per hundred cubic centimeters. Wassermann tests of the spinal fluid and the blood elicited negative reactions. The acid

phosphatase content was 1.8 and the alkaline phosphatase content 6.6 Bodansky units.

The nonprotein nitrogen content was 37 mg. per hundred cubic centimeters, and the total serum protein content was 5.4 Gm. per hundred cubic centimeters, with an albumin fraction of 3.1 Gm. There was mild leukocytosis, and a 5 per cent eosinophilia was found on all occasions. The serum calcium content was 10.4 mg., the inorganic phosphorus content 4.4 mg. and the cholesterol content 263 mg. per hundred cubic centimeters. The urine was normal at all times, and Bence-Jones protein was never found. The vital capacity was 4,800 cc., and the electrocardiogram was normal.

Roentgenologic Studies.—Roentgenograms of the skull (fig. 1) revealed two bony defects, one in the left parietal bone, just above the occipitoparietal suture and the other in the occipital bone, near the site of the torcular Herophili. Small

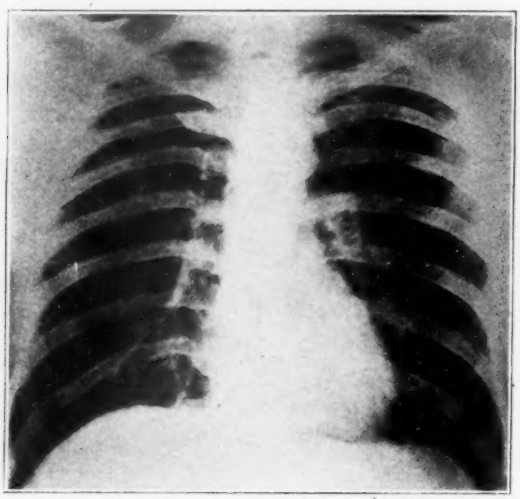

Fig. 6.—Roentgenogram of the chest, April 1945, showing striking decrease in infiltration of the lung.

areas of destruction were found in the left ilium and pubis (fig. 2). An early lesion in the body of the third lumbar vertebra was detected elsewhere in February 1943. A subsequent examination in March 1943 at Vanderbilt University Hospital revealed the fully established defect (fig. 3). No pathologic change was noted in roentgenograms of the long bones, hands and feet. A roentgenogram of the chest (fig. 4) revealed a fine nodular type of infiltration in the upper halves of both fields of the lungs.

Diagnosis.—The general well-being of this patient, the multiple skeletal lesions and the apparent absence of any primary malignant focus made a diagnosis of metastatic malignant growth unlikely. There was no Bence-Jones proteinuria to support a diagnosis of multiple myeloma. A clinical diagnosis of eosinophilic granuloma of bone was ventured, and it was thought that the pulmonary pattern did not conform to any well known disease, nor did it suggest any unusual con-

dition such as sarcoid, histoplasmosis or Loeffler's syndrome. This patient's mild but persistent eosinophilia, although not a constant finding in other reported cases, was also consistent with a diagnosis of eosinophilic granuloma of bone.

Biopsy.—On Feb. 6, 1943, the lesion in the left parietal region was explored (Dr. Walter Dandy) at the Johns Hopkins Hospital. The normal bone in this region had been replaced by tissue of a whitish yellow color having the consistency of cream cheese. This was removed with a curet. It was noted that the dura at the base of the bony defect was not involved.

Microscopic Examination.—The curetted tissue was seen to consist chiefly of histiocytes, large cells with a single irregularly shaped nucleus and a pale pink

Fig. 7.—Roentgenogram taken in December 1943, showing healed lesion in third lumbar vertebra.

cytoplasm (fig. 5). None of these cells contained sufficient fat to be classed as "foam cells" or lipophages. A few were undergoing necrosis. There were many focal accumulations of eosinophils. Small round lymphocytes and plasma cells were scattered diffusely throughout the tissue, save for one or two areas of fairly dense lymphocytic infiltration. There was a decided increase in fibrous connective tissue and some proliferation of the endothelium to form new capillaries.

Treatment and Further Course.—The mild headache and backache and a troublesome nonproductive cough had continued to cause him considerable dis-

comfort. On March 22, 1943, the roentgenologic studies were repeated as a preliminary to radiation therapy. In addition to the lesions noted previously, which had not changed, there was a well outlined area of destruction in the body of the third lumbar vertebra (fig. 3) approximately 1.5 cm. in diameter.

Roentgenologic therapy was started on March 22, and the first series of treatments was completed on April 6. Divided doses of 300 r (with backscatter) were given with 200 kilovolts and 20 milliamperes through 0.5 mm. of copper and 1 mm. of aluminum filtration at a distance of 50 cm. and through suitable-sized portals for each field. The skull was treated through an occipital field angled through the lesions of the occipital and posterior parietal areas on one day. On the second day the anterior portals of the right and left lungs were treated, and on the third day the posterior part of the left ilium to the lower part of the lumbar region of the spine and the anterior fields of the symphysis pubis were treated. This rotation of treatment through the portals was followed until a total of 1,500 r

Fig. 8.—Roentgenogram of pelvis, December 1943, showing partial healing of lesions in the left side of the ilium and those around the symphysis pubis. Several gas shadows are present below the lesion in the left side of the ilium. A new lesion is present in the right superior side of the iliac spine.

to each was administered. The posterior fields of the right and left lungs each received 600 r. On July 15, 16 and 17, daily doses of 500 r were given to the left ilium and hip through the anterior, lateral and posterior portals, in rotation. On December 9, 10 and 11, daily doses of 400 r were administered to the left lower molar region. On Oct. 16, 1944, a single dose of 500 r was given to the new lesion in the posterior part of the right ilium.

Although the roentgen ray evidence of resolution of the lesions was not soon apparent, there was prompt relief of the aching pains of which the patient had previously complained. In addition, the cough disappeared.

On June 18, 1943, roentgen ray examination of his skull, spine, chest and pelvis revealed evidence of healing of the lesions in the left ilium, pubis and third lumbar vertebra. The defects in the skull were essentially unchanged. The small nodular infiltrations in the lungs had decreased considerably in size (fig. 6). About

a month later, the lesion in the third lumbar vertebra was almost completely healed, as were the lesions in the pubis (figs. 7 and 8). In December 1943, the patient complained of pain in the left jaw. Roentgen ray examination revealed a small area of destruction in the left mandible. Similar lesions have been reported.[2] On Oct. 16, 1944 there was also a new lesion in the crest of the right ilium. It was noted that the healing process was progressing in the old lesions.

In April 1945, the bony defect at the site of curettage was seen to be essentially unchanged, whereas the other lesion in the skull had almost completely healed. The lesions elsewhere exhibited much improvement. The tardiness of the healing process in the curetted lesion is at variance with the results reported by others.

COMMENT

The benign character of this patient's course has persisted to date. He has maintained his weight and usual vigor and has been actively engaged in the practice of law. There has been no fever, in contrast to several reported cases in which, because of severe pain, local signs of

Tabulation of Data by Mallory[7]

I. Letterer-Siwe's disease	(Reticuloendotheliosis; aleukemic reticulosis; nonlipid histiocytosis) Children under 2 years Fever; skin rash; anemia; purpura; splenomegalia Histologically: proliferation of monocytes and clasmatocytes in bone, skin, lymph nodes and spleen, with or without deposits of lipids
II. Hand-Schüller-Christian syndrome	Older children Defects in cranial bones; exophthalmos; diabetes insipidus Xanthoma deposits with or without eosinophils Associated lymph nodes may show typical eosinophilic granuloma, with or without deposits of cholesterol
III. Eosinophilic granuloma	Children and adults Single or multiple lesions of the bone Good general health; low grade fever; leukocytosis with eosinophilia; local tumor, sometimes painful Histologically: granuloma with eosinophils Cured by local excision, roentgen rays or occasionally spontaneously

inflammation, fever and leukocytosis, it was difficult to rule out Ewing's tumor of bone. This particular situation was notable in the case recently reported by Solomon and Schwartz.[3] There has been no involvement of the long bones with the threat of spontaneous fracture as noted in a report of a case by Versiani and others.[4]

We are unable to state with certainty that the nodular infiltration of the lungs observed on roentgen ray examination is a visceral mani-

2. Bailey, J. W., and Freis, E. D.: Eosinophilic Granuloma of Bone with Manifestations in Jaw, J. Am. Dent. A. **31**:91-94 (Jan.) 1944.

3. Solomon, H. A., and Schwartz, S.: Eosinophilic Granuloma of Bone, J. A. M. A. **128**:729-731 (July 7) 1945.

4. Versiani, O., and Junqueira, M. A.: Hand-Schüller-Christian's Syndrome and "Eosinophilic or Solitary Granuloma of Bone," Am. J. M. Sc. **207**:161-166 (Feb.) 1944.

festation of this disorder, which has hitherto been described as involving only bone, even though irradiation of the pulmonary fields produced a decided improvement in the lungs and was associated with disappearance of cough. However, in consideration of the fundamental similarity of eosinophilic granuloma of bone, Hand-Schüller-Christian disease and Letterer-Siwe's disease (as stressed by Jaffe and Lichtenstein,[5] Green and Farber,[6] Mallory[7] and others), such a possibility does not seem remote (table).

CONCLUSION

A case of eosinophilic granuloma of bone is reported, characterized by multiple skeletal lesions and a coexistent nodular pulmonary infiltration.

The latter is believed to be a visceral (pulmonary) involvement as a part of the general picture of eosinophilic granuloma of bone. If this is true, this is the first such case reported. This fact together with the multiplicity of the lesions of the bones, prompted this publication.

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5. Jaffe, H. L., and Lichtenstein, L.: Eosinophilic Granuloma of Bone: Condition Affecting One, Several or Many Bones, but Apparently Limited to Skeleton, and Representing Mildest Clinical Expression of Peculiar Inflammatory Histiocytosis Also Underlying Letterer-Siwe's Disease and Schüller-Christian Disease, Arch. Path. **37**:99-118 (Feb.) 1943.

6. Green, W. T., and Farber, S.: "Eosinophilic or Solitary Granuloma" of Bone, J. Bone & Joint Surg. **24**:499-526 (July) 1942.

7. Mallory, T. B.: Medical Progress. Pathology: Diseases of Bone, New England J. Med. **227**:955-960 (Dec. 10) 1942.

INDUCED MALARIA OF FOREIGN ORIGIN

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IT IS the purpose of this report to describe certain features of induced malaria as observed in the treatment of 243 patients with neurosyphilis. The establishment by the Surgeon General of a center for the treatment of neurosyphilis in a hospital to which numerous patients with naturally acquired malaria had been admitted from overseas provided a unique opportunity to study the transmission of Plasmodium vivax malaria under controlled conditions. It also afforded a means of observing the untreated primary malarial attack with respect to symptoms, complications, course, response to antimalarial therapy and rate of relapse.

MATERIAL AND METHODS

The 243 patients included in this study were suffering from asymptomatic (77 per cent) or symptomatic (23 per cent) neurosyphilis. One hundred and seventy-five of these patients were white and comprised the chief group for study. The remaining 68 patients were Negroes; 45 of these were given quartan malaria, and an effort was made to transmit tertian, or P. vivax, malaria to the other 23 patients. The 243 patients ranged from 19 to 50 years of age, the majority being in the third and fourth decades of life. Careful physical evaluation of each patient revealed no contraindication to malarial therapy.

One group of patients was inoculated by means of laboratory bred Anopheles mosquitoes [1] infected with P. vivax. This group will hereafter be referred to as the group with "mosquito-induced" malaria. The mosquitoes had been previously infected from patients with relapsing P. vivax malaria, contracted in the Pacific or the Mediterranean area. Another group of patients was infected by intravenous inoculation of blood (usually 7 cc.) containing the trophozoites of the same strains of P. vivax. A third group was infected by inoculation of blood

From the Army Service Forces, Eighth Service Command, Harmon General Hospital, Longview, Tex.

1. Ehrman, F. C.; Ellis, J. M., and Young, M. D.: Plasmodium Vivax Chesson Strain, Science **101**:377 (April 13) 1945. Young, M. D.; Stubbs, T. H.; Moore, J. A.; Ehrman, F. C.; Hardman, N. F.; Ellis, J. M., and Burgess, R. W.: Studies in Imported Malarias: Ability of Domestic Mosquitoes to Transmit Vivax Malarias of Foreign Origin, J. Nat. Malaria Soc. **4**:127 (June) 1945.

containing a Trinidad strain of Plasmodium malariae producing quartan malaria.[2] The majority of the last group were Negroes.

Blood smears were examined daily for malarial parasites. With the patients who had been bitten by infected mosquitoes the taking of smears was begun six days later. When a positive thick smear was found or when signs or symptoms of malaria developed, the patient was transferred to the malaria ward. With the patients who had been inoculated intravenously with blood, daily examination of smears began the day after inoculation.

The routine care of the patient after admission to the malaria ward can be summarized as follows: In general, he was kept in bed unless he was feeling well enough, when afebrile, to be up and about the ward. Accurate notes were kept with reference to his temperature, his intake and urinary output of fluids, his blood pressure and his weight. Urinalyses were done twice weekly, and complete blood counts and determinations of blood nonprotein nitrogen, at weekly intervals. A general diet was given to the patient if his temperature was below 100 F. If it was above 100 F. and if the patient had the inclination to eat, he was given a diet of soft foods or liquids, high in vitamins and calories. Taking of fruit juices and eggnogs between meals was encouraged. Intravenous infusions of dextrose in saline solution were given liberally, particularly when the patient had been vomiting or when it was apparent that his intake of fluids for the day was inadequate (i. e., less than 3,500 cc.).

The patient was routinely given 5 grains (0.32 Gm.) of ferrous sulfate three times a day, 2 multivitamin capsules daily and 1 Gm. of sodium chloride three times a day. When the patient began to have a chill, blankets were applied for comfort. No hot water bags were used for warmth. Beginning either with the chill or with the first recording of a temperature of 100 F., the temperature, the pulse rate and the respiratory rate were recorded every half hour until the temperature fell below 100 F. Barbiturates and codeine were used to control restlessness and severe headache. A physical examination, partial or complete, was made every other day, or more frequently if indicated. A record of the patient's symptoms and of physical findings was kept on special forms so that the data could be analyzed easily.

The patient was allowed to have paroxysms until he accumulated at least forty hours of fever with the temperature at 104 F. or over. In almost all instances, eight or more paroxysms were necessary in order to accomplish this. In certain instances a spontaneous remission of fever and other symptoms occurred with or without the disappearance of parasitemia. Some of the patients who tended to have fever of the quotidian type were given 0.1 Gm. of Thio-bismol intramuscularly, in an effort to convert the fever into a tertian type. In general, this was accomplished when the Thio-bismol was given from sixteen to twenty-four hours before the expected paroxysm.[3] This was done for two reasons: First, fever of the quotidian type exhausted the patient much more rapidly than did that of the tertian type. Second, when fever of the tertian type was maintained, one "brood" of parasites had sufficient time to develop gametocytes before the fever treatment was terminated. The development of adequate gametocyte levels allowed the infection of additional lots of mosquitoes with the malarial strains under study. In a few instances it was necessary to bring the malaria

2. This strain of P. malariae was supplied by Dr. Mark Boyd, Tallahasse, Fla.

3. Mayne, B., and Young, M. D.: The Technic of Induced Malaria as Used in the South Carolina State Hospital, Ven. Dis. Inform. **22**:271 (Aug.) 1941.

therapy to an end with quinacrine hydrochloride because of a complication, e. g., jaundice or extreme exhaustion.

RESULTS

Table 1 gives the data pertaining to the transmissions of malaria by blood inoculations and by mosquito bites. It will be noted that the transmission of P. vivax, or tertian, malaria by the bites of mosquitoes was highly successful in the white patients (99 per cent successes) but relatively unsuccessful in the Negro patients (83 per cent failures) even with several attempts at inoculation.

The difficulty in transmitting domestic strains of P. vivax to Negro patients is well known [3] ; whether it is an inherent racial characteristic

TABLE 1.—*Transmissions of Tertian and Quartan Malaria*

	Race	Guadalcanal	New Guinea	Mediterranean
I. By Mosquitoes Infected with P. Vivax				
Number of strains transmitted.....	.....	4	8	3
Number of patients with neurosyphilis	White	13	62	26
Number of patients inoculated.....	White	101	..	..
	Negro	23	..	..
Number of patients inoculated successfully, with development of tertian malaria	White	99*	99%	..
	Negro	4†	17%	..
II. By Blood Containing Trophozoites of the Same Strains of P. Vivax as in I‡				
Number of strains transmitted.....		2	2	2
Number of patients with neurosyphilis inoculated..		4	50	17
Number of patients inoculated successfully.....		4(100%)	48(96%)§	17(100%)
III. By Blood Containing a Trinidad Strain of P. Malariae Induced				
Number of patients inoculated successfully, with development of quartan malaria.....				48¶
Number of patients inoculated unsuccessfully.....				3

* Nine of these patients had to be inoculated more than once.

† Of the 19 "failures," all were inoculated more than once.

‡ All of the patients in this group were white, and the group represents the initial attempt at inoculation.

§ See comment in text.

¶ This includes 3 white patients.

or whether it has been conditioned by previous exposure to P. vivax malaria cannot be judged from our data. It can be stated, however, that this racial difference in response to inoculation was not due to technical factors. The high percentage of successful transmissions shown by the white patients (99 per cent) attests the excellent technic used by the members of the United States Public Health Service in charge of those transmissions.[1] The results which we obtained in the Negro patients with foreign strains of P. vivax are in disagreement with the statement of Butler and Sapero [4] that American Negroes are very susceptible to Pacific strains.

4. Butler, F. A., and Sapero, J. J.: Postwar Tropical Disease Problems in the United States, South. M. J. **38**:459 (July) 1945.

Altogether, 71 attempts were made to transfer P. vivax to white patients by blood transfusions, and 69 of them were successful. The 2 instances of failure are deserving of comment. Both patients had acquired P. vivax malaria while overseas. The first had his last attack sixteen days, and his last dose of suppressive quinacrine hydrochloride twelve days, before the attempted inoculation. He was observed for seventeen days, and the inoculation was considered unsuccessful. He was then reinoculated with the same strain, and malaria developed in twelve days. Whether this attack was brought about by the second inoculation or whether it was a relapse of the naturally acquired malaria cannot be stated. The second patient had his last malarial attack thirty-five days before the attempted inoculation. Malaria developed twenty-five days later and without further inoculation. Since truly successful inoculations have not been observed by us to have such prolonged incubation periods (table 2), it seemed reasonable to assume that the inoculation was unsuccessful and that the patient suffered a relapse of his naturally acquired malaria.

Forty-eight patients, 45 Negro and 3 white, were successfully inoculated with P. malariae, producing quartan malaria. In only 3 patients were the inoculations unsuccessful. No efforts were made to transmit by mosquito bites the parasites producing quartan malaria.

Prepatent[5] *and Incubation*[6] *Periods Following Inoculation.*—Although rather large variations occur in the prepatent and the incubation periods in different persons, it will be noted that the averages for these intervals show little difference between the different strains of P. vivax. Since data are not available as to the degree of infection in the mosquitoes, no definite conclusion can be drawn from any of the slight, though statistically significant, differences noted. It can be stated generally that an average of two weeks elapses before signs of malaria appear after mosquito inoculation of imported strains of P. vivax. In this study the shortest time noted for the development of clinical malaria after the bite of the mosquito was eight days; the longest, twenty days. Apparently, when the sporozoite form of the parasite is introduced into the human host by the mosquito, at least eight days are required before erythrocytic forms appear in sufficient numbers to be seen or to produce symptoms. This is in definite contrast to the finding that on several occasions after the introduction of the trophozoite forms of the parasite by blood inoculation clinical malaria with visible parasitemia developed one day after the inoculation. In general, however, a period of four to five days was required. Again, as in the groups with

5. The prepatent period is defined as the period between the time of inoculation and the time of development of parasitemia as revealed in a malarial smear.

6. The incubation period is defined as the period between the time of inoculation and the time at which the temperature rises above 100 F.

mosquito-induced malaria, there were rather wide individual variations, the reasons for which are not obvious.

As is well known, the incubation period for quartan malaria is characteristically longer than that for tertian malaria. In this series and with the same method of inoculation the incubation period was at

TABLE 2.—*Prepatent and Incubation Periods in P. Vivax, or Tertian, Malaria*

	Number of Cases Analyzed	Prepatent Period *		Incubation Period	
		Range, Days	Average, Days	Range, Days	Average, Days
I. Mosquito-Induced Malaria					
Source of strains:					
Guadalcanal	15	10-19	12.9±0.4	11-20	14.3±0.4
New Guinea	53	8-19	13.5±0.2	8-19	14.2±0.2
Mediterranean	22	9-14	12.2±0.2	11-16	13.1±0.2
II. Blood-Induced Malaria					
Source of strains:					
Pacific	54†	1-11	4.2	1-16	4.5
Mediterranean	17	1-12	5.1	1-12	5.1
Trinidad (quartan)	40	6-35	15.5	6-35	15.5

* The lowest density of parasitization which may be recognized by examination of a smear is approximately 10 parasites per cubic millimeter (Boyd [17]).

† All but four of these were of the New Guinea strain.

TABLE 3.—*Incidence of Usual Clinical Manifestations in Patients with Primary Attacks of P. Vivax Malaria Who Were Not Treated*

	Pacific Malaria (101 Patients), per Cent	Mediterranean Malaria (35 Patients), per Cent
Headache	98	100
Backache	98	100
General aches	90	94
Weakness	97	100
Nausea	85	77
Vomiting	72	63
Diarrhea	17	17
Cerebral symptoms	13	8
Tinnitus	31	28
Abdominal pain, right side	33	14
Abdominal pain, left side	51	25
Abdominal pain, none	48	63
Abdominal tenderness, right side	25	17
Abdominal tenderness, left side	63	45
Abdominal tenderness, none	30	48
Spleen palpated	72	57
Liver palpated	62	34
Herpes labialis	48	40

least ten days longer. This finding is in agreement with the statements of Mayne and Young [3] and of others.

The Course of the Infection.—(*a*) Clinical Features: As stated previously, an effort was made to allow the patient to experience forty hours of fever with the temperature 104 F. or higher as the therapeutic minimum. This was achieved in from nine to twenty-eight days, with

an average of eighteen days, for P. vivax, or tertian, malaria, and in from fourteen to thirty-one days, with an average of twenty-two days, for quartan malaria. From eight to fifteen paroxysms were required to obtain the desired result. Certain patients, however, never attained the desired amount of fever, because a spontaneous remission aborted the attack. This interesting phenomenon will be commented on later.

Table 3 lists the most common clinical symptoms and signs of the untreated patients with primary attacks of P. vivax, or tertian, malaria. No patients with quartan malaria were included in this analysis. The features noted are not considered as complications of the disease since they appeared to be characteristic of the infection itself. Headache, backache, generalized aching and varying degrees of weakness were present in practically all the patients whether the disease was of Pacific or of Mediterranean origin. Gastrointestinal complaints also were common; nausea and vomiting were present in about three fourths of the patients during some period of the illness. Abdominal pain, usually in the upper quadrant, and tenderness appear to be somewhat less frequent in malaria of Mediterranean origin than in that of Pacific origin, but the number of patients studied in detail in the former group was small. Tinnitus was noted in more than one fourth and herpes labialis in almost half of the patients. It would seem that in some patients suffering from natural malaria the auditory disturbances which have been noted and attributed to gunfire or to the administration of quinine may have been due to the malarial infection itself.

Hepatic enlargement and splenic enlargement were common and were noted somewhat more frequently in malaria of Pacific origin. In an analysis of the frequency with which splenic and hepatic enlargement occurred during the promptly treated acute attacks of naturally occurring relapsing P. vivax malaria of Pacific origin, it was found that the spleen was palpable in only 23 per cent and the liver in 11 per cent.[7] The fact that in the total series splenomegaly and hepatomegaly were noted in 72 and 62 per cent of the patients, respectively, is accounted for by the longer duration of the untreated illness. In figure 1 it will be noted that the longer the period of malarial activity the more likely was the spleen or the liver to be palpable.

Cerebral symptoms were noted in at least 10 per cent of all patients and appeared to be of no more serious import than those seen in any other severe febrile illness. In other words, no patients could be considered to manifest the features of "cerebral malaria" caused by P. falciparum infections. In all patients the cerebral symptoms disappeared

7. Gordon, H. H.; Lippincott, S. W.; Marble, A.; Ball, A. L.; Ellerbrook, L. D., and Glass, W. W., Jr.: Clinical Features of Relapsing Plasmodium Vivax Malaria in Soldiers Evacuated from the South Pacific Area, Arch. Int. Med. **75**:159 (March) 1945.

as soon as the body temperature fell to normal levels. A semistuporous state or mild mental confusion was the most usual symptom; however, delirium was noted in 2, and unconsciousness in 3, different patients.

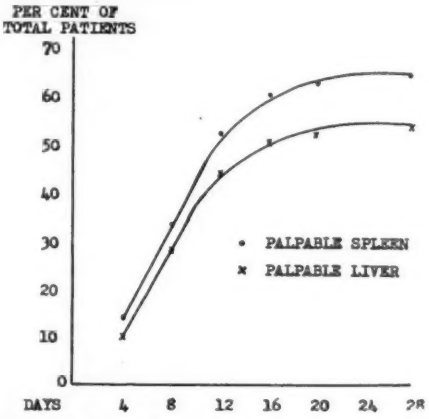

Fig. 1.—The relation of the occurrence of hepatomegaly and splenomegaly to the duration of the illness.

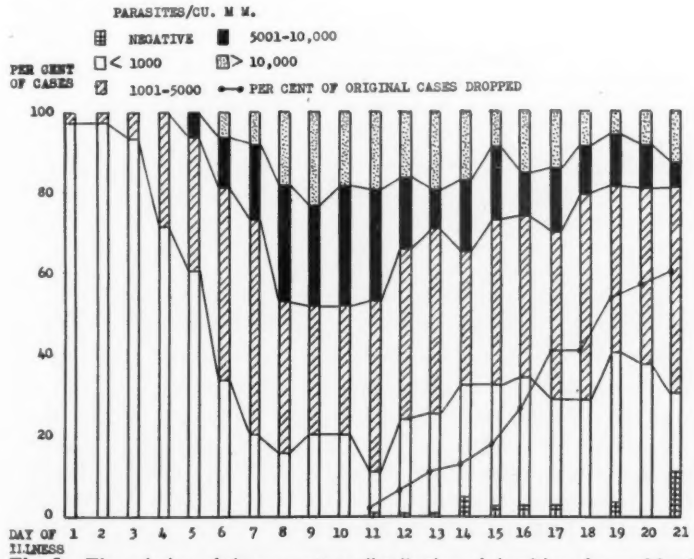

Fig. 2.—The relation of the percentage distribution of densities of parasitization of the blood to the day of disease in sporozoite-induced Pacific P. vivax malaria.

(*b*) Degree of Parasitemia: A careful analysis was made regarding the trend of the densities of the parasitizations in 46 patients. These

patients had been mosquito-inoculated with Pacific strains of P. vivax, and in this group no effort had been made to influence the course of the infection in any way—e. g., by the administration of Thio-bismol. Figure 2 shows in graphic form the data obtained. On the first day that the parasites were observed in smears, only 4 patients had a sufficient degree of parasitemia to allow an actual count; the remaining 42 patients had merely "positive thick smears." It will be noted that after the second day a fairly rapid rise occurred in the parasite counts, so that a peak was reached by about the eleventh day. Thereafter there was a gradual but definite fall. This is more easily seen in figure 3, in which the data on density of parasitization are presented as total averages rather than as percentage distribution. The data were not analyzed beyond a three week period, since by this time in over half the cases the desired therapeutic effect had been reached and the patients

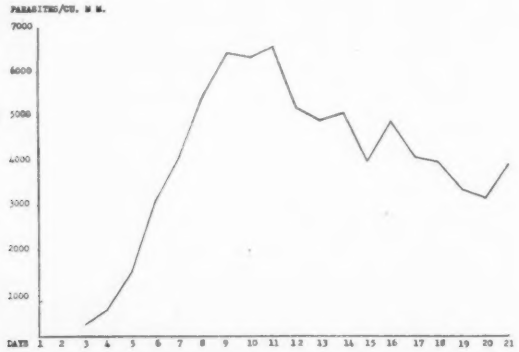

Fig. 3.—The relation of average densities of parasitization to the day of disease in sporozoite-induced Pacific P. vivax malaria.

had been started on quinacrine hydrochloride, leaving too few cases for analysis. It appears that most persons suffering from the primary attack of tertian malaria acquire some degree of immunity after the first few days of the infection, shown by the fall in parasitic densities.[8]

(*c*) Occurrence of Spontaneous Remissions: As stated by Boyd, Kiepper and Matthews,[9] varying degrees of immunity or susceptibility will be indicated by the responses of patients to inoculation. Earlier in the paper it was mentioned that only a small percentage of the Negro

8. Taliaferro, W. H., and Taliaferro, L. G.: Active and Passive Immunity in Chickens Against Plasmodium Lophurae, J. Infect. Dis. **66**:153, 1940; The Effect of Immunity on the Asexual Reproduction of Plasmodium Brasilianum, ibid. **75**:1, 1944.

9. Boyd, M. F.; Kiepper, W. H., and Matthews, C. B.: A Deficient Homologous Immunity Following Simultaneous Inoculation with Two Strains of Plasmodium Vivax, Am. J. Trop. Med. **18**:521, 1938.

patients were successfully inoculated with P. vivax. Presumably those persons in whom inoculation failed possess the highest degree of immunity. In figure 4 are shown typical examples of varying degrees of clinical tolerance of the malarial parasites. The first patient had "positive thick smears" for four days, underwent one mild malarial paroxysm and then not only became completely asymptomatic but possessed sufficient immunity to cause the visible parasitemia to disappear. The other patient had a spontaneous remission after six satis-

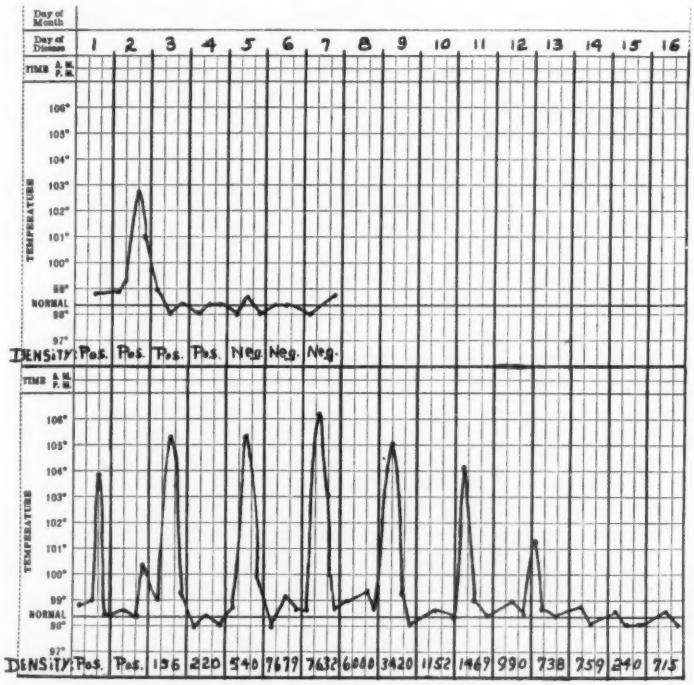

Fig. 4.—Two examples of spontaneous remissions in induced P. vivax malaria.

factory paroxysms although still maintaining fairly good densities of parasitization. In fact, these densities were as great as, or greater than, those observed earlier in the illness while good paroxysms were occurring. Apparently the occurrence of the malarial paroxysms depends more on the presence or the absence of immune mechanisms and/or the stage of development of the parasite than on the number of parasites present in the blood. This is supported by the fact that we were unable to demonstrate a significant correlation between the number of hours of fever on any given day and the density of parasitization. The variable rela-

tion between parasitic density and number of paroxysms has been discussed for P. falciparum malaria by Kitchen.[10]

In an effort to determine whether or not a previous attack of malaria played any part in the development of the spontaneous remission, careful past histories were obtained from the 172 patients inoculated with P. vivax. The data thus obtained are shown in table 4. Spontaneous remissions were observed more than three times as frequently in those who gave a past history of malaria than in those who did not. Therefore, it seems reasonable to believe that previous attacks of malaria may confer a certain degree of immunity as manifested by spontaneous remissions. However, that this immunity was incomplete is shown by the fact that it was possible to transmit the infection to almost all the white patients.

TABLE 4.—*The Relation of Spontaneous Remissions to a Past History of Malaria in One Hundred and Seventy-Two White Patients Successfully Inoculated with P. Vivax*

	Total	Number Having Remission	Per Cent Having Remission
Without past history of malaria	145	31	21
With past history of malaria	27	19	70

Since this Army hospital was located in the southern part of the United States, where malaria is more or less endemic, and since there was a certain regional admission of patients with neurosyphilis, a higher percentage (16 per cent) of our patients gave a past history of malaria than might be observed in other parts of the country. Twenty-two of the 27 patients with such a history had had malaria during civilian life, usually many years prior to the course of therapeutic malaria. It seems that once a certain degree of tolerance of the malarial parasites is developed it is not soon lost but may persist for many years. Of the 5 patients who had acquired malaria naturally during their Army career, 2 underwent a spontaneous remission during the course of therapeutic malaria.

Complications.—In table 5 are summarized the complications noted in both the tertian and the quartan forms of malaria. Of 172 patients suffering from untreated P. vivax malaria, 28 had albuminuria (16 per cent). None of these had albumin graded more than "2 plus" (on a scale of 4) in their urine, and the presence of albumin was not associated with occurrence of abnormal elements in the urinary sediment

10. Kitchen, S. F.: The Infection in the Intermediate Host, Symptomatology, Falciparum Malaria, in A Symposium on Human Malaria, Publication 15, American Association for the Advancement of Science, 1941, p. 196.

or with evidence of renal insufficiency. Furthermore, with termination of fever the albuminuria disappeared.

However, 3 Negro patients suffering from quartan malaria had moderate azotemia, marked albuminuria and hyaline and granular casts in the urinary sediment. In none did hypertension, evident edema, retinal change or anemia develop. All 3 patients had normal urine on two examinations and normal levels of nonprotein nitrogen in the blood before the fever began, and none gave a past history of disease of the urinary tract. One of these patients had to be transferred to another hospital twelve days after the termination of the fever therapy. At the time of transfer albumin and formed elements were still present in the urinary sediment, although the nonprotein nitrogen of the blood had fallen from a maximum of 120 mg. per hundred cubic centimeters to

TABLE 5.—*Complications Noted During the Course of Therapeutic Malaria*

	P. Vivax, or Tertian, Malaria (172 Patients)		Quartan Malaria (48 Patients)	
	Number	Per Cent	Number	Per Cent
Albuminuria (benign)	28	16	..	..*
Jaundice	8	5	1	2
Severe anemia (red blood cell count below 3,000,000)	11	7	(No record)	
Urticaria	4	2	0	0
Dependent edema	2	1	0	0
Hiccups	3	2	0	0
Dendritic corneal ulcer	1	0.5	0	0
Pulmonary tuberculosis	1	0.5	0	0
Uremia	0	0	3	7
Deaths	0	0	0	0

* Records are available for only 15 patients; 4 were shown to have transitory albuminuria. In the urine of 1, however, albumin did not completely disappear and is still present in slight amounts, two and a half months after making its appearance. This patient also was shown to have moderate elevations of blood cholesterol level (375 and 400 mg. per hundred cubic centimeters), but there were no evidences of nitrogen retention, edema or inability to concentrate the urine.

normal and the blood cholesterol was 150 mg. per hundred cubic centimeters. Subsequent data on this patient are not available. However, the second patient first showed abnormal urine after eight paroxysms, and the nonprotein nitrogen in the blood rose to a maximum of 120 mg. per hundred cubic centimeters seven days later. A pure culture of the gonococcus was obtained from the urine, but the exact focus of infection was not determined. There was no urethral discharge; the prostate was normal on examination, and after a later course of penicillin the urine no longer yielded positive cultures. However, before the penicillin treatment was started and after the antimalarial treatment with quinacrine hydrochloride was instituted, the albuminuria disappeared and the nonprotein nitrogen in the blood fell to normal levels. It appears that the renal insufficiency was due to the malaria rather

than to the infection of the urinary tract. Likewise, the azotemia appeared to be of renal origin and not "extrarenal," since evidences of renal damage were so conspicuous in the urine and since the blood pressure and the fluid balance appeared to be maintained throughout the illness.

In the third patient the abnormal findings appeared after the second malarial paroxysm; the nonprotein nitrogen in the blood was 50 mg. per hundred cubic centimeters three days later and rose to a maximum of 130 mg. ten days after the appearance of albuminuria and five days after the quinacrine therapy was started. In contrast to the second patient, the third patient had azotemia associated with a moderate suppression of urinary output and a fall in specific gravity of the urine for four days prior to the maximal azotemia. The urinary output ranged from 660 to 1,060 cc. on intakes of 3,360 to 4,560 cc. per day. The patient was not having fever during this period, and edema was not evident. With intravenous injection of fluids and the disappearance of malarial parasites from the blood cells as shown by examination of smears, the nonprotein nitrogen gradually fell to normal. Three and one-half weeks later the patient was completely asymptomatic, although he still had moderate albuminuria and was unable to concentrate urine to a specific gravity above 1.020. The blood cholesterol values determined after the nonprotein nitrogen had reached normal levels were 300 and 261 mg. per hundred cubic centimeters, and the values for serum proteins were normal. Apparently, in the patients studied quartan malaria was more apt to cause serious renal damage than was tertian malaria. The incomplete data available on these patients do not warrant speculation as to the nature of the renal lesion. However, Kitchen [11a] and Meleney [11b] have both pointed out that a picture of the nephrotic syndrome is sometimes observed in patients suffering from chronic quartan malaria and more rarely in those suffering from P. vivax malaria. It is reported that in some of the patients with renal involvement the disease has gone on to a fatal termination despite antimalarial therapy. Also, Giglioli, cited by Meleney, observed 5 patients with quartan malaria who died and who presented the picture of chronic glomerular nephritis with nitrogen retention.

Recognizable jaundice occurred in 8 patients with P. vivax, or tertian, malaria and in 1 patient with quartan malaria. The jaundice appeared from nine to twenty-five days after the onset of the illness. On its appearance, the fever was terminated with quinacrine hydrochloride. In all the cases the jaundice appeared to be due to hepatitis directly caused by the malarial infection. The liver was enlarged and

11. (*a*) Kitchen, S. F.: The Infection in the Intermediate Host, Symptomatology, Quartan Malaria, in A Symposium on Human Malaria, Publication 15, American Association for the Advancement of Science, 1941, p. 190. (*b*) Meleney, H. E.: The Physiological Pathology of Malaria, ibid., p. 223.

tender; bile was present in the urine, and the direct van den Bergh test showed an immediate or delayed reaction. In 1 instance the jaundice developed when there was a spontaneous remission of his fever, but the blood smears revealed evidence of malaria. In all instances, terminating the infection and giving the patient supportive treatment (dextrose solutions intravenously, extra amounts of vitamins, a high protein diet) resulted in rather rapid disappearance of the jaundice and the enlargement of the liver. In table 6 are given the available data from the studies of hepatic function in these patients. A detailed report on changes in hepatic function in patients with induced malaria has been presented recently by Fredricks and Hoffbauer,[12] and the results of other studies will be considered in detail in a separate communication.

In most of the patients there was moderate anemia (the number of red blood cells ranging between 3,000,000 and 4,000,000 per cubic millimeter), but severe anemia (red cell counts less than 3,000,000) was noted in only 11 of the patients with P. vivax malaria. In 1 patient the anemia and the exhaustion were of sufficient degree to warrant a blood transfusion. We have no accurate data concerning the rate of disappearance of the anemia since the patients were given a three week convalescence furlough after they had received complete treatment with quinacrine hydrochloride. However, in most instances normal erythrocyte counts were observed on the patients' return to the hospital.

Generalized urticaria was noted in 4 patients. It was not particularly severe, nor was it associated with edema of the glottis. In all instances it made its appearance within the first five days of illness and disappeared within three days.

Edema of the ankles was noted in 2 patients. In 1 of these patients the serum proteins were determined and were found to be somewhat below normal; the total protein was 5.5 Gm., the albumin 2.7 Gm. and the globulin 2.8 Gm. per hundred cubic centimeters. In this patient mild jaundice was noted about the same time that edema of the ankles appeared. After the fever therapy was discontinued and the patient's general condition improved, the jaundice and the edema disappeared. At no time did the patient have albumin in his urine. The hypoproteinemia may have been due to hepatic damage and/or diminution of the intake of protein.

Severe hiccups developed in 3 patients. The cause was not entirely clear, but in all there was moderate abdominal distention. The hiccups were controlled by morphine, warm stupes to the abdomen and neostigmine bromide after the usual measures failed to bring relief.

12. Fredricks, M. F., and Hoffbauer, F. W.: A Study of Hepatic Function in Therapeutic Malaria, J. A. M. A. **128**:495 (June 16) 1945.

TABLE 6.—*Summary of Results of Tests of Hepatic Function in Eight Patients Who Contracted Clinical Jaundice During Fever Therapy with P. Vivax Malaria*

Patient	Initial Studies *						During Fever									After Fever						Clinical Evidence of Hepatic Disease
													Liver									
	I. I.	S. B.	Brom.	Hipp.	Galact	Uro.	I. I.	S. B.	Brom.	Hipp.	Galact.	Uro.	Enl.	Ten.	Vomiting	I. I.	S. B.	Brom.	Hipp.	Galact.	Uro.	
L. L.....	5	0.1	Trace	..	0.45	1:5	50	8.0	..	..	..	1:100	2+	2+	0	7	0.4	3	..	0.2	1:5	None
C. L.....	7	0.2	2	..	0.71	1:5	80	8.1	..	..	..	1:100	2+	2+	Yes	..	...	2	..	1.0	1:20	None
C. M.....	5	0.3	2	..	0.56	1:5	60	2.5	40	..	..	1:200	1+	2+	Yes	8	1.0	2	..	..	...	None
V. V.....	10	1.0	Trace	..	1.65	1:20	35	2.0	..	..	..	1:100	1+	1+	0	7	2.0	Neg.	..	...	1:5	None
E. H.....	9	0.7	4	0.9	....	...	30	2.0	32	0.23	0.59	.....	1+	1+	0	..	...	2	..	...	...	None
A. B.....	7	0.2	2	1.0	....	...	36	2.2	36	0.3	..	.....	1+	1+	0	..	...	2	0.58	...	...	None
C. W.....	..	...	.....	..	....	...	50	2.8	..	..	..	.....	2+	0	Yes	..	...	..	..	...	...	None
J. D.....	..	...	.....	..	....	...	80	5.6	..	..	..	.....	1+	0	0	..	...	..	..	...	...	None

* The icterus index (I. I.) is recorded in units and the serum bilirubin (S. B.) in milligrams per hundred cubic centimeters. The sulfobromophthalein sodium retention (Brom.) is recorded as per cent retained in the specimen of blood taken forty-five minutes after the injection of 5 mg. of the dye per kilogram of body weight. The hippuric acid tolerance is recorded as the gram of hippuric acid present in the specimen of urine collected for one hour following the intravenous injection of 1.77 Gm. of sodium benzoate. The galactose tolerance (Galact.) is reported as the amount of galactose excreted in the urine during a five hour period after the ingestion of 40 Gm. of galactose. The urobilinogen excretion (Uro.) is recorded as the concentration in a single morning specimen of urine.

In 1 patient a dendritic ulcer of the cornea developed, which persisted for three weeks after the cessation of fever. It is interesting that this patient did not have associated herpes of the lip.

One patient contracted acute pulmonary tuberculosis during the course of the fever therapy. This was the most serious complication encountered. The patient had a normal chest before beginning treatment, according to a roentgenogram taken at that time. A small exudative lesion was discovered during a routine roentgenologic examination one month after the malaria therapy was terminated.

No deaths have occurred in this series of patients. Moore [13] reported, from his own experience and from a survey of the literature, a mortality rate of from 1 to 2 per cent among selected patients given P. vivax malaria. Fong [14] reported a mortality rate of 2.9 per cent among patients treated with quartan malaria. That we were fortunate enough not to have any deaths can be accounted for by the fact that most of the patients were young, healthy men whose neurosyphilis was asymptomatic and also by the fact that careful examinations were made to rule out renal, hepatic or cardiac disease and adequate care given during the course of the fever.

Rate of Disappearance of Parasites with Quinacrine Hydrochloride.—When adequate malarial therapy had been completed, all the patients were treated with quinacrine hydrochloride. The dosage was essentially as previously described,[15] namely, 0.8 Gm. the first twenty-four hours and 0.4 Gm. each twenty-four hours for five subsequent days, so that a total of 2.8 Gm. was given in six days. By the second day—i. e., forty-eight hours after the beginning of therapy—96 per cent of the patients had become afebrile. It is noted from figure 5 that practically all the patients (96 per cent) suffering from P. vivax malaria, whether this was mosquito induced or blood induced, had negative smears by the third day—i. e., seventy-two hours after the beginning of antimalarial therapy. In an analysis of data on 111 patients with induced P. vivax malaria in whom the actual density of parasitization was known the day prior to starting antimalarial therapy it was found that, in general, those patients with lower densities had negative smears before those with higher densities. This is shown in figure 6 and is similar to what is found in studies of naturally acquired P. vivax malaria of foreign origin.[16] It is also of interest that only 21 per cent of smears

13. Moore, J. E.; Kemp, J. E., and others: The Modern Treatment of Syphilis, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1943, p. 389.

14. Fong, T. C. C.: Therapeutic Quartan Malaria in Therapy of Neurosyphilis Among Negroes, Am. J. Syph., Gonor. & Ven. Dis. **24**:133, 1940.

15. Treatment of Clinical Malaria and Malarial Parasitemia, Bull. U. S. Army M. Dept. **4**:284 (Sept.) 1945.

(Footnotes continued on next page)

were free of parasites twenty-four hours after treatment was begun (fig. 5), compared with 51 per cent in a group of patients with relapses of the naturally acquired disease.[16] This is probably due to the higher percentage (46 per cent) of patients with parasitic densities

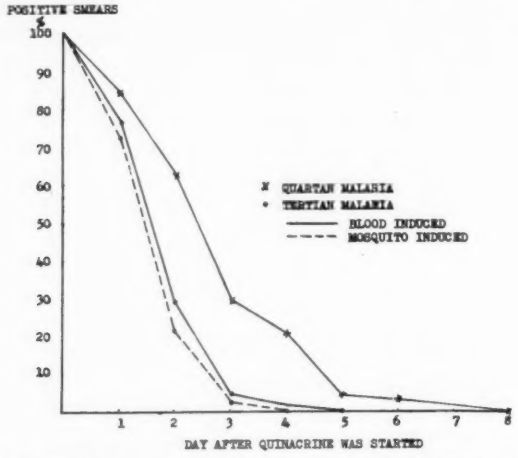

Fig. 5.—The rate of disappearance of parasites with administration of quinacrine hydrochloride in the customary dosage.

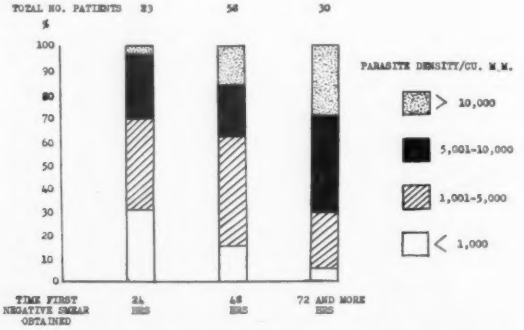

Fig. 6.—The relationship of parasitic density before treatment to the time at which the first smear free of parasites was obtained.

above 5,000 per cubic millimeter in this study, compared with 22 per cent among patients with naturally acquired malaria.[16]

Figure 5 also reveals that visble parasitemia is definitely slower in its disappearance in patients having quartan malaria than in those

16. Gordon, H. H., Christianson, H. B., and Lippincott, S. W.: A Comparison of Quinine and Quinacrine in the Treatment of the Clinical Attacks of Vivax Malaria, South. M. J. **39**:631 (Aug.) 1946.

having tertian malaria. For example, by the third day of quinacrine therapy almost all patients suffering from tertian malaria had negative smears while approximately 30 per cent of those with quartan malaria still had positive smears. In fact, for 1 patient the quinacrine therapy had to be continued past the sixth day, and the smears did not become free of parasites until the eighth day. Unfortunately, actual densities of parasitization are not available for this group of patients. The existence of this difference in response to quinacrine may reside in biologic differences between the two species of parasites. This is believed to be true because much higher densities are encountered in tertian (P. vivax) than in quartan (P. malaria) malaria.[17]

Relapse Rates of Induced Malaria.—No data were obtained on the relapse rates of quartan malaria. In table 7 is given a summary of

TABLE 7.—*Relapses Following Quinacrine Treatment of Induced P. Vivax Malaria of Foreign Origin*

	Total Number of Patients	Number of Patients Who Relapsed *	Per Cent of Patients Who Relapsed	Observation Period of Nonrelapsers, Days
Pacific "Mosquito-induced"	69	45	65	109 (66-185)
Pacific "Blood-induced"	28	0	0	106 (66-165)
Mediterranean "Mosquito-induced"	16	2	13	113 (61-162)
Mediterranean "Blood-induced"	4	0	0	82 (64-95)

* No patient was considered a nonrelapser unless he had been followed for at least sixty days after completion of quinacrine therapy.

information in regard to P. vivax malaria. These data are discussed in more detail in a separate report.[18] Suffice it to state that no relapses were observed in the group with blood-induced malaria, while a relapse rate of 65 per cent was recorded for the group with mosquito-induced infection, similar strains of P. vivax of Pacific origin being used. This indicates, as has been well known for other strains, that the introduction of trophozoites of Pacific P. vivax was not followed by a relapsing disease but the introduction of sporozoites was. In a small group of 16 patients with mosquito-induced malaria of Mediterranean origin there were only 2, or 13 per cent, relapses within the period of observation. Apparently, within the period noted, Mediterranean malaria did not have the same stubborn tendency to relapse as Pacific malaria.

17. Boyd, M. F.: Present Day Problems of Malaria Infections, J. A. M. A. **124**:1179 (April 22) 1944.

18. Gordon, H. H.; Marble, A.; Engstrom, W. W.; Brunsting, H. A., and Lippincott, S. W.: Relapses Following Delayed Treatment of Naturally Induced Vivax Malaria of Pacific Origin, Science **103**:391 (March 29) 1946.

SUMMARY AND CONCLUSIONS

In 195 patients (172 white and 23 Negro) with neurosyphilis attempts were made to transmit Plasmodium vivax malaria by mosquito bites or by inoculation of blood. The strains transmitted were of Pacific and Mediterranean origin.

The attempts to transfer P. vivax malaria whether by mosquito bites or by inoculation of blood were highly successful in white patients, whether they gave a past history of malaria or not, and relatively unsuccessful in Negro patients. However, a spontaneous remission of fever was observed more than three times as frequently in those who gave a past history of malaria as in those who did not.

The prepatent [5] and incubation [6] periods averaged about two weeks when mosquitoes, and five days when blood, was used in the transmission of the infection.

It was noted that as the disease progressed the concentration of parasites in the blood at first rapidly increased but after the eleventh day began to fall.

Sixty-five per cent of the patients inoculated by mosquitoes infected with Pacific strains of P. vivax had relapses, while no patients relapsed who had been inoculated intravenously with blood containing the same strains.

Quartan malaria was transmitted to 48 patients (45 Negro and 3 white) by inoculation of blood containing P. malaria. Quartan malaria differed from tertian (P. vivax) malaria not only in the longer interval between paroxysms but also in the longer period of incubation, the slower response to quinacrine therapy and the tendency to cause serious renal complications.

No deaths were seen in this series of patients.

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ACTINOMYCOTIC ENDOCARDITIS

Report of Two Cases with a Review of the Literature

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CARDIAC involvement produced by Actinomyces is not frequently reported in medical literature. Cornell and Shookhoff [1] have presented a comprehensive review of 68 cases. Recapitulation of such a review is not within the scope of this paper. Actinomycotic endocarditis without trace of related disease in any other part of the body is rare.

REVIEW OF THE LITERATURE

Jervell [2] reported a case of endocarditis with the etiologic agent determined as a leptothrix which was recovered in pure culture from the blood.

The patient was a 20 year old man with a history of rheumatic fever at 12 years of age and with cardiac involvement on subsequent occasions. Three weeks before the last admission to the hospital, acute gastroenteritis developed, followed by symptoms of pyemia and myelitis. Ecchymosis and numerous petechiae appeared in various organs. Systolic and diastolic murmurs were present, and extra systoles occurred. The urine contained albumin, pus, blood and urobilin. In the laboratory it was not possible to recover from the urine the gram-positive rods in pure culture. A blood count showed 70 per cent hemoglobin (Sahli), 4,200,000 erythrocytes per cubic millimeter and 20,000 leukocytes per cubic millimeter. Spinal puncture revealed a slightly cloudy fluid with about 150 cells per cubic millimeter, of which about 50 per cent were lymphocytes and 50 per cent were polymorphonuclear leukocytes. Tests for albumin and globulin were positive. Cultures were sterile. Ophthalmoscopic examination of the eyegrounds produced evidence of "Embolia art. retinae" near the macula lutea of the left eye. This was associated with paracentral scotoma. Weakness and then paresis of both legs developed. Urinary incontinence occurred. There was pain about the nates and the anus. Anesthesia was present from the lumbar region downward. Babinski's reflex was present. Various neurologic examinations showed shifting signs from time to time. Before death, complete right-sided hemiplegia developed with aphasia and coma. The patient died about six weeks after the onset of illness.

An anatomic summary of the autopsy revealed: "Endocarditis verrucosa valv. mitralis et aortae. Hypertrophia et dilatatio cordis. Haemorrhagia punctatae (et emollitio) cerebri. Embolia art. fossae Sylvii dext. Infarctus et abscessus lienis.

From the Board of Health Laboratory, Gorgas Hospital, Ançon, Canal Zone.

1. Cornell, A., and Shookhoff, B.: Actinomycosis of the Heart Simulating Rheumatic Fever, Arch. Int. Med. **74**:11-27 (July) 1944.

2. Jervell, O.: Leptotrix i blodet ved et tilfælde av malign endokardit, Norsk mag. f. lægevidensk. **83**:36-46, 1922.

Infarctus renis sin. Degeneratio parenchym. hepatis." All three aortic leaflets and both mitral leaflets showed verrucous vegetations. Ulcerations were present in association with the lesions of the mitral leaflets. Sections of valvular lesions showed gram-positive rods. The author considered the possibility of the symptoms of myelitis being associated with the emboli present in the medulla.

Plate cultures of blood showed small gray-white colonies with faint zones of hemolysis. Microscopically, the organism occurred as gram-positive rods. Broth cultures showed the organism developing gram-positive filaments without ramifications. The organism was aerobic and did not grow anaerobically. The rods were referred to as small, almost simulating streptococci, for which they were first mistaken. Micro-organisms similar to those of the blood cultures were recovered from the lesions of the heart valves and the spleen, but not in pure culture. Cultures were inoculated into guinea pigs, white mice and rabbits, without results.

Alestra and Girolami[3] reported 2 cases with the clinical picture of subacute endocarditis, in neither one of which was there any evidence of a portal of entry.

The first patient was an 18 year old barber with a previous history of having had intermittent fever from 8 to 10 years of age, at which time pleurisy of the right side developed. After this incidence, fever did not recur, and the patient remained in good health except for dyspnea on exertion. At 18 years of age he had an attack of sore throat, malaise, chills, fever and palpitation. The spleen was palpably enlarged. A roentgenogram of the heart showed particular enlargement of the left border. A blood count showed 18,000 leukocytes per cubic millimeter, 81 per cent of which were polymorphonuclear leukocytes. Two blood cultures were positive for the same type of organism, which occurred as greenish brown pinpoint colonies, similar in appearance to those of Streptococcus viridans. The colonies were similar microscopically to those in broth cultures. The organism took a gram-variable stain and appeared as cocci, streptococci, coccobacilli, rods and filaments. No branching forms were seen. Subcultures failed to show growth, and anaerobic cultures were not carried out. The authors expressed the belief that they were dealing with a streptothrix, although they mentioned that the organism was not studied completely, because of its failure to grow.

The patient was treated with iodides. He also received a total of 480 cc. of Septojod (a preparation of iodine for parenteral use) intravenously. No fever developed at the end of treatment, and the spleen was no longer palpated. The systolic murmur had become louder. He was followed for two years, during which there was no development of illness. After this period he was lost.

The second patient was a 37 year old woman employed as a clerk, with the history of having had sore throat on two occasions two years apart. She was treated with diphtheria antitoxin. At 11 years of age she was told by a physician that she had a congenital heart disease. At 13 years of age she had exudative pleurisy on the right side. After this she was in good health up to the age of 25. At this time she had an attack of palpitation, cyanosis of the face, tremors and dizziness. She never lost consciousness. The attack was of short duration and was followed by headaches. At 32 years of age she experienced sore throat, fleeting pains, chills and sweats. The sore throat cleared up in eight days under treatment with salicylates. Later palpitation and cardiac arrhythmia with extra

3. Alestra, L., and Girolami, M.: Endocarditi da nocardie, Policlinico (sez. med.) **44**:441-463, 1937.

systoles developed. When she was 37 years old, she experienced anorexia, general malaise, a sudden severe pain in the left side of the chest and a few days later a fever. She was given a proprietary 1 per cent solution of sodium iodide intramuscularly; fever and sore throat persisted, although the thoracic pain disappeared. The heart was enlarged transversely. An intensive systolic thrill was present over the midsternal line and was palpated in the second intercostal space. The blood pressure was 98 mm. of mercury systolic, and 65 diastolic. A blood count showed 24,000 leukocytes per cubic millimeter. Progressive cardiac impairment developed, and the patient died about five months after the onset of the last illness, with a clinical diagnosis of subacute endocarditis with congenital heart disease. She had received sulfonamide drugs by mouth, sodium salicylates, Prontosil (the hydrochloride of 2,4-diaminoazobenzene-4-sulfonamide), a total dose of 100 cc. of Septojod intramuscularly, arsenical preparations and cardiotonics.

Autopsy showed hypertrophy of the right ventricle and vegetative endocarditis involving the pulmonary valves and conus. The borders of the defects showed thickening consistent with previous endocarditis. Patency of the interventricular septum was present below the aortic ring. A small anemic pulmonary infarct and pleurisy with adhesions were also present. Microscopically, the endocardium was infiltrated with small thrombi. The vegetations showed small abscesses and groups of coccal forms and bacillary elements.

Five blood specimens cultured showed pinpoint gray colonies that developed in four hours, after which no further development occurred. Subcultures, however, in dextrose agar showed moist firm white colonies that were adherent to the medium. These had a greenish color on plain agar. Microscopically, the organism occurred as cocci, arranged in groups and in chains, from some of which elongated and fusiform structures extended. Bacillary forms and straight and flexed filaments were present. Some filaments contained granules along their entire extent and stained as if composed of gram-positive cocci in gram-negative filaments. The organism took a gram-variable stain.

A culture was inoculated into guinea pigs and rabbits. The animals died within twenty-four hours. The same organism was recovered in culture from the animals. The authors considered this organism as "Nocardia."

Uhr [4] observed endocarditis due to Actinomyces bovis in a 24 year old Jewish man. No other focus of infection was found to suggest a portal of entry.

The patient became ill with pain in both calves, nausea, vomiting and malaise, followed by fever, chills and sweats. A short systolic murmur was localized over the apex. The heart rate was 120. The cardiac sounds were forceful and regular. During his stay in the hospital the systolic murmur became aggravated. Petechiae and larger purpuric lesions developed over various parts of the body. The sensorium became clouded, and coma ensued. The patient died thirty-five days after the onset of illness. Treatment consisted of supportive measures, transfusions, administration of oxygen and intravenous injection of sodium diiodide, which was discontinued in absence of adequate response.

Four separate blood specimens cultured while the patient lived yielded a pure culture of A. bovis. The organism grew only in presence of blood and was microaerophilic. It required reduced oxygen tension for isolation. Culturally, the organism showed up as "tangled threads of mycelium." Older cultures showed

4. Uhr, N.: Bacterial Endocarditis: Report of a Case in Which the Cause Was Actinomyces Bovis, Arch. Int. Med. **64**:84-90 (July) 1939.

many abnormal structures. The organism was not acid fast and was gram positive. The strain was not pathogenic for rabbits.

At autopsy the mitral valve presented a large soft friable yellowish vegetation which principally involved the aortic cusp, but small clusters were also along the line of closure. The anterior and posterior surfaces of the cusps of the mitral valve were involved for some distance. There was no evidence of previous valvulitis. The left auricle showed a small vegetative endocardial lesion, but there was no evidence of an old rheumatic auricular lesion. Microscopic section of the spleen showed "a bacterial clump" in an arteriole. Cultures of the crushings of the mitral lesion showed A. bovis.

Basu [5] mentioned a strain of Actinomyces recovered from the blood stream of a patient on the ninth day of an illness with high fever and patches of bronchopneumonia in both lungs. This was an aerobic organism which produced no lesions in rabbits.

Cornell and Shookhoff [1] referred to a case diagnosed clinically as one of rheumatic heart disease in both the Norwegian Hospital and the Montefiore Hospital, where the patient was observed for several months. Autopsy revealed myocardial and pericardial actinomycosis. This involvement, however, was by extension from the original source in a diverticulum of the esophagus.

REPORT OF CASES

CASE 1.—A 37 year old married white man, born in Minnesota, had been on the Isthmus of Panama for twenty-nine months in the capacity of switchboard operator at Gatun Hydroelectric Power Station. He was admitted to a Canal Zone hospital, Dec. 26, 1942, with marked pallor, discrete small nontender palpable nodes in both inguinal regions, elevated temperature and a rasping systolic murmur over the apex of the heart. This murmur was faintly transmitted along the sternum. No enlargement of the heart was evident, and no arrhythmia was noted. The blood pressure was 110 mm. of mercury systolic and 70 diastolic. No petechiae were observed. The previous personal history was negative except for growing pains in the legs for one month at the age of 6 years. The family history was noncontributory. A diagnosis of acute bacterial endocarditis was made; the blood cultures, however, were sterile.

Course in Hospital.—First Admission: After the patient's temperature had been of the spiking type for four days, sulfathiazole therapy was started. His temperature began to fall, although it remained somewhat elevated for the following ten days. It then remained normal for a week, after which the administration of sulfathiazole was discontinued. At this time his temperature rose slightly for three days; then it dropped to normal and remained normal for two weeks. After this it became elevated again. With administration of sulfathiazole, the temperature fell to normal and remained normal for two weeks. Such courses continued throughout the patient's stay in the hospital, and the bouts of fever were controlled by sulfathiazole, which was last given on June 15, 1943. With the exception of a slight rise on two different occasions, his temperature remained normal until the date of discharge.

5. Basu, C. C.: Notes on a New Strain of Actinomyces Obtained by Blood Culture, Indian J. M. Research **25**:325-327, 1937.

The systolic murmur changed in character and intensity during the first three days. A diastolic murmur developed on the fourth day. This murmur was predominant for several weeks, after which it disappeared and only a rough systolic murmur remained.

Petechiae occurred in the conjunctivas on January 4. Several other petechiae occurred during the next few weeks, but after that time no more appeared during this hospitalization. The spleen was never palpated.

The patient gained weight and voiced no complaints except for occasional mention of painful spots on fingers and a heel. The tonsils were removed on March 3. At one time urinary suppression developed, after hematuria from sulfathiazole, but the condition improved with discontinuation of the drug. Leukopenia occurred on several occasions, but this disappeared with cessation of the drug.

All laboratory tests gave values within the normal range except for the weekly readings of the sedimentation rate, which was high up to May 6, 1943, when it became normal, and for leukopenia and hematuria associated with a drug reaction.

The patient was discharged on July 7, although he was not considered cured. At home he received sulfathiazole intermittently, to control the bouts of recurrent fever.

Second Admission: On November 1, the patient was admitted to Gorgas Hospital for a survey by the medical examining board. The blood pressure was 120 mm. of mercury systolic and 70 diastolic. No cardiac enlargement or arrhythmia was noted. A prolonged blowing systolic murmur was present over the entire precordium. The patient was again having bouts of fever, with his temperature rising to 102 F. He showed good response to sulfathiazole, 2 Gm. of which was given as an initial dose and 1 Gm. three times a day to attain a total of 69 Gm. in three different courses. The pulse rate varied between 70 and 118. The respiration remained normal.

Laboratory examination showed a rapid sedimentation rate on three different occasions (60, 60 and 90 mm. in one hour in the Westergren tube). The hemogram showed: 4,550,000 erythrocytes per cubic millimeter, 13.5 Gm. of hemoglobin (Sahli) per hundred cubic centimeters, a hematocrit reading of 40, a mean corpuscular volume of 87.9 cubic microns, a mean corpuscular hemoglobin value of 29.7 micromicrograms, a mean corpuscular hemoglobin concentration of 33.8 per cent, a color index of 0.873 and a volume index of 0.915. Two leukopenic counts were reported (3,000 and 4,000 leukocytes per cubic millimeter). A fragility test showed beginning hemolysis in 0.44 per cent sodium chloride solution and complete hemolysis in 0.30 per cent solution. Two specimens of urine showed red cells on microscopic examination and were positive for albumin. One specimen showed finely granular casts. Several specimens revealed a few pus cells. Repeated blood cultures were sterile. An electrocardiogram showed right axis deviation and notching in the P wave in all leads. All other laboratory tests failed to give positive information.

At this time, December 14, the patient was discharged with the diagnosis of "valvular heart disease, mitral; subacute endocarditis, cause undetermined; blood cultures, sterile."

Third Admission: On March 4, 1944 the patient was readmitted to a Canal Zone hospital because sulfathiazole was having no further effect on the course of the disease. At this time the patient was well developed, though thin and pale, and appeared chronically ill. The blood pressure was 130 mm. of mercury systolic and 60 diastolic. He was not as alert mentally as previously, but he was conscious and oriented. A half dozen petechiae were found on the palms. Numerous petechiae were present in the conjunctivas. The lungs showed no

abnormality. The heart did not appear enlarged, and it had a slow rate and a regular rhythm. Harsh, rough systolic and early diastolic murmurs were distinctly audible over the apex. The rest of the physical examination showed nothing remarkable.

The hemoglobin was 60 per cent (Sahli) repeatedly. The erythrocyte count ranged between 3,000,000 and 4,000,000 per cubic millimeter. The leukocyte count ranged between 7,150 per cubic millimeter on the day of admission and 26,000 per cubic millimeter on March 20, 1944, with differential counts of 39 per cent polymorphonuclear leukocytes and 57 per cent lymphocytes, and 98 per cent polymorphonuclear leukocytes and 2 per cent lymphocytes, respectively. The urine repeatedly showed albumin (4 plus), casts (4 plus), around 20 pus cells per high power field, and many red cells. Of a total of 11 blood cultures, 6 were sterile and 5 were contaminated. The contaminants were in part possibly due to transportation of cultures on the train. The Kahn test was negative. The nonprotein nitrogen was 53.4 mg. per hundred cubic centimeters of blood. The sedimentation rate was 84 mm. in forty-five minutes. The spinal fluid was reported to have a normal sugar content, 2 plus protein, 204 cells per cubic millimeter, of which 95 per cent were lymphocytes and 5 per cent polymorphonuclear leukocytes, and a pressure of 270 mm. of water. Cultures were sterile.

During this last stay in the hospital the patient received 51 Gm. of sulfadiazine by mouth and ten separate doses of 50 cc. of a 2.5 per cent solution of sulfadiazine intravenously in nine days. Six transfusions of 250 cc. each were given. The heart murmurs were aggravated, and the number of petechiae increased greatly. The temperature ranged between 97.4 F. and 105.2 F. It showed a daily rise and drop, with the peak mostly around 103 F. and the low point around 99.0 F. The pulse rate was for the most part around 120, but it reached as high as 160 before death, on March 27, 1944.

Postmortem Diagnoses.—The following diagnoses were abstracted from the protocols and associated with more detailed elaboration in reference to the organs chiefly involved.

The anatomic diagnoses were: vegetations of the mitral valve, large, acute, ulcerative; acute focal myocarditis; endocardial wrinkling, extensive; myocardial fibrosis; cardiac hypertrophy, 400 Gm.; pulmonary edema, bilateral; infarcts of the spleen with abscess formation; infarct of the ileum with abscess formation; infarcts of the kidneys; multiple punctate hemorrhages of the kidneys; acute and subacute focal glomerulonephritis, bilateral; acute and subacute pyelonephritis, bilateral; petechial hemorrhages of the conjunctivas, the buccal mucous membranes, the skin of the neck, extremities and trunk, the mucosal surfaces of the epiglottis, larynx and trachea, the pleurae, the parietal pericardium and the mucosal surface of the bladder; subarachnoid hemorrhages, diffuse; chronic passive congestion of the liver, early; icterus, slight; accessory spleen, attachment to tail of pancreas.

The microscopic diagnoses were consistent with the anatomic. In addition, hepatic and myocardial abscesses were diagnosed.

The cause of death was subacute bacterial endocarditis.

Smears, Blood Chemistry, Serologic Tests and Routine Cultures.—Smears from the vegetation of the heart revealed "gram-positive short-chained cocci." Blood chemistry showed, per hundred cubic centimeters of blood, 155.8 mg. of nonprotein nitrogen, 121.6 mg. of urea nitrogen, 8.3 mg. of creatinine and less than 30 mg. of glucose. Acid phosphatase was 5.7 units (King and Armstrong), and alkaline phosphatase was 18.9 units, per hundred cubic centimeters of serum. The Kahn test of the blood and the Wassermann test of the spinal fluid were negative. Cultures of blood and urine were sterile. Cultures of an abscess of the brain

were contaminated. Cultures of the spinal fluid showed Staphylococcus aureus (hemolytic), possibly a contaminant from the autopsy room. Cultures from the vegetation of the mitral valve are described later.

Gross Pathologic Observations.—The brain was swollen and edematous, with flattened gyri and shallow sulci. Numerous punctate hemorrhages were scattered through all lobes, most prominent in the frontal lobes. Small hemorrhages were present in the basal ganglions. An area of softening, measuring 1.5 cm. in its greatest dimension, was located superficially in the right lateral occipital region. This area was hemorrhagic and contained a small amount of creamy yellow pus.

The heart (fig. 1 *A*) was slightly enlarged, weighing 400 Gm.. The apex lay opposite the fifth interspace, 9 cm. to the left of the midsternal line. The epicardium was smooth and glistening. There were several subepicardial petechiae. The myocardium was diffusely red-brown and firm. Here and there small, dark gray areas were present, indicating fibrosis. There was no evidence of infarction. The appearance of the chambers of the left side of the heart was greatly distorted by a vegetation which was attached to the auricular surface of the anterior cusp of the mitral valve. At its base the vegetation was firmly attached and occupied a region on the cusp measuring 3.5 cm. in the circumferential dimension and 1.0 to 2.5 cm. in width. It was soft and friable and extended into the chamber of the heart as a large fungating mass measuring 3.0 cm. in depth. At its base it was firm and gave the impression of long-standing attachment, but the peripheral parts were soft and friable and appeared to have been formed rapidly and recently. A small soft pinkish yellow vegetation, measuring 0.5 by 0.5 cm., was found on the posterior cusp of the mitral valve. The entire auricular surface of the mitral valve was swollen and moderately firm, but the tiny firm fibrous vegetations of rheumatism were not present. The chordae tendineae were not blunted. Extensive wrinkling was present in the endocardium of the left auricle, and the possibility of a rheumatic background for the valvular lesion was considered. The other valves were not affected. The circumferential valvular measurements were as follows: aortic valve, 6.5 cm.; mitral valve 10.0 cm.; tricuspid valve, 14.0 cm.; pulmonary valve, 6.5 cm. The left ventricular wall measured 2.1 cm., the right ventricular wall 0.6 cm. and the interventricular septum 2.0 cm. in thickness.

The kidneys (fig. 1 *A*) were similar in size and appearance, measuring 16 by 9 by 4.5 cm. The capsules stripped easily. The surfaces and the parenchyma of each kidney contained many punctate hemorrhages, so that they had a flea-bitten appearance. Several wedge-shaped firm grayish red infarcts were present in each kidney, and most of these contained irregular abscesses. The parenchyma was pale, grayish pink, soft and pliable. The cut edges everted; both kidneys were swollen and edematous. The corticomedullary boundaries were distinct. The calices and the pelves were not dilated, and the ureters were patent.

The entire gastrointestinal tract showed numerous small punctate hemorrhages. A reddish gray submucosal abscess, measuring 1.3 cm. in its greatest dimension, was located in the distal portion of the ileum.

The greater portion of the spleen (fig. 1 *A*) was friable and of a red-brown color. Approximately the lateral one half of the organ showed an area of irregular outline, firm consistency and gray-pink color, consistent with an old infarct, in which were several small pus pockets.

Microscopic Observations.—(*a*) Brain (fig. 4 *B, C* and *D*): A section taken from the right frontal lobe and stained with hematoxylin and eosin showed generalized areas of mild necrosis, evidenced by the variable amount of loss of distinctness of cytologic outline. One area extending into the cortex from the periphery of the section showed an eosinophilic amorphous coagulum.

A section taken from the lower portion of the right occipital lobe showed a thickening of the leptomeninges with areas of diffuse hemorrhage associated with diffuse cellular infiltration in which polymorphonuclear leukocytes, fewer lymphocytes and some macrophages participated, a few of the last-named being laden with a deep golden pigment. Fibrin was scattered throughout, evidenced by

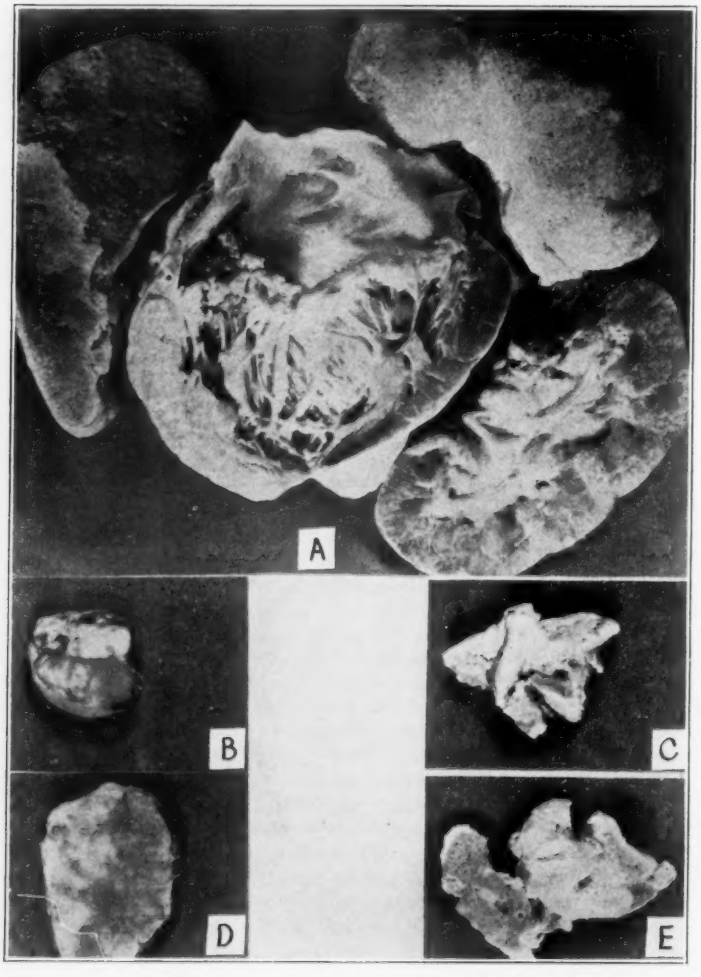

Fig. 1 (case 1).—*A*, gross autopsy specimens: the heart, the kidneys and the spleen. Note the vegetations on the mitral valve.

B and *C*, lymph node and lung, respectively, or a rat inoculated with a culture from the involved valve.

D and *E*, lymph node and lung, respectively, of a rat inoculated with Actinomyces grown from a sulfur granule in another case.[6]

eosin-staining strands. Mild fibroblastic proliferation was present through various areas. The inflammatory reaction was most marked in the perivascular areas. There were focal areas of microscopic abscesses in the cortical tissue, evidenced by aggregations of cells, predominantly polymorphonuclear cells, with a few lymphocytes and macrophages. Some of these abscesses were definitely perivascular, with the small vessels intact. Other areas in the section showed degenerative changes of the vessel wall, evidenced by eosinophilic foci of hyalinization. Some fields showed variable amounts of fibrin in the perivascular areas. One vessel showed complete occlusion of its lumen by basophilic cocci, cocci in chains, and rods (fig. 4 *B*). There was a mild perivascular infiltration of polymorphonuclear leukocytes, lymphocytes and macrophages in this region. The first mentioned cells predominated. Some of the other abscesses showed an occasional basophilic rod. Gram's stain (MacCallum's modification of Goodpasture's method) of the section showed the coccal structures and the rods to take a purple stain, and they were less distinctly observed with this stain.

A section taken from the occipital abscess and stained with hematoxylin and eosin showed extensive areas of cortical necrosis, hemorrhage and abscess formation, illustrated by the loss of outline of structural detail of cortical tissue and blood vessels in these areas, together with eosinophilic zones of hyalinization. Some of these areas were also associated with hemorrhage, presence of fibrin and extensively diffuse cellular infiltration, predominantly polymorphonuclear leukocytes together with some lymphocytes and macrophages, some of which were laden with a deep golden brown pigment. Focal clumps of basophilic cocci, cocci in chains, and rods were seen scattered through the collection of polymorphonuclear cells. Gram's stain showed these clumps of cocci and rods to take both a purple and a basophilic stain in this section.

(*b*) Heart: A section of the mitral valve (fig. 2 *A*) stained with hematoxylin and eosin showed an eosinophilic border of variable width, which was focally and diffusely infiltrated with basophilic clumps and clusters that assumed a variable pattern under low magnification. These patterns will be described in detail subsequently. The basophilic masses extended into the border and toward the base of the lesion. Areas of focal and diffuse cellular infiltration, polymorphonuclear leukocytes together with fewer monocytes, were also present in the border. These cells showed degenerative changes, observed in the loss of distinctness of structural outline. The outer border was covered in areas by focal and mildly diffuse infiltrations of degenerated polymorphonuclear leukocytes and fewer monocytes, together with fine eosinophilic fibers in some parts. The free border also showed areas of breaks of continuity of outline exposing the basophilic groups of clumps and clusters.

The connective tissue stroma adjacent to the border described showed areas of focal and diffuse abscess formation, evidenced by collections predominantly of polymorphonuclear leukocytes and fewer monocytes with basophilic vesicular nuclei and eosinophilic cytoplasm. Several of these cells were degenerated. A definite fibroblastic proliferation, together with the described inflammatory reaction, was present in the connective tissue stroma, which also showed fatty ingrowth in other areas, particularly around the blood vessels. The adjacent cardiac muscle bundles revealed nothing remarkable, but the supportive connective tissue stroma of these fasciculi showed areas of mild focal infiltration, polymorphonuclear leukocytes in association with a few monocytes with basophilic vesicular nuclei and eosinophilic cytoplasm.

Scrutiny of the valve section stained with hematoxylin and eosin with the oil immersion objective of the microscope (fig. 2 *C, D, E* and *F*) showed the afore-

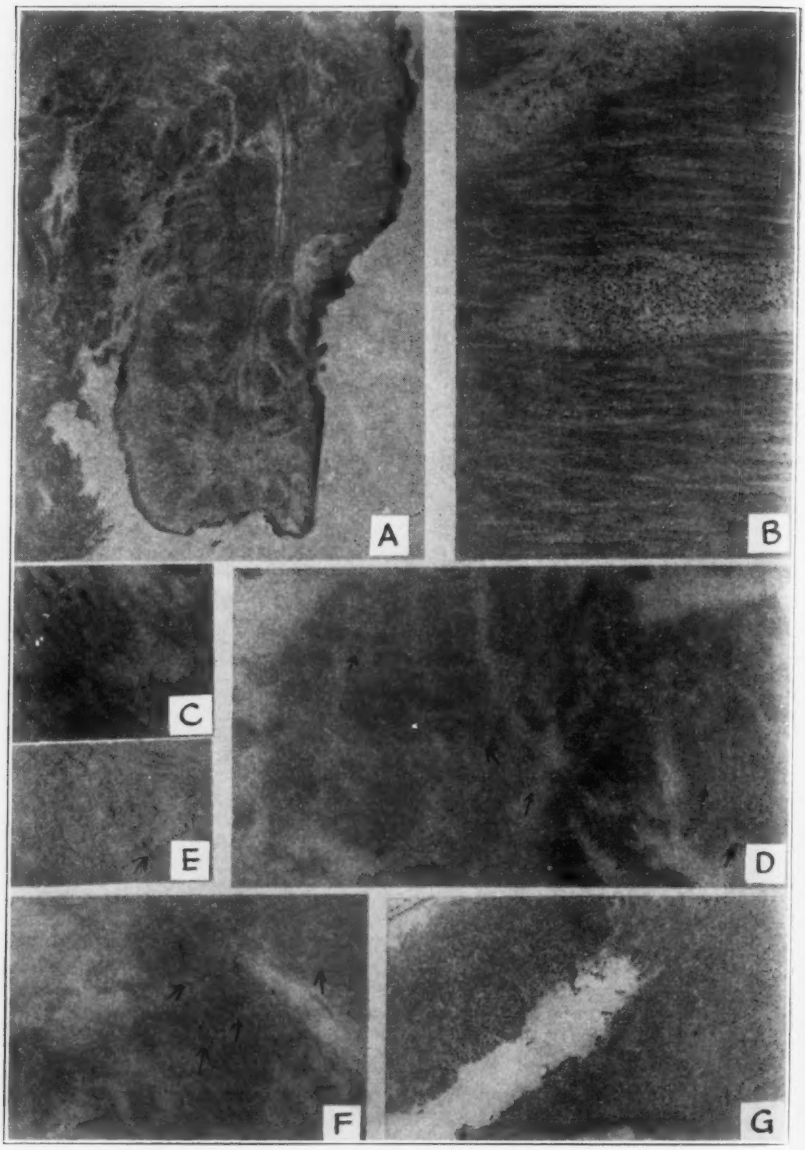

Fig. 2 (case 1).—*A*, section of the involved mitral valve (hematoxylin and eosin stain; × 75).

B, papillary muscle of the heart showing an abscess (hematoxylin and eosin stain; × 75).

C, *D*, *E* and *F*, various areas of the valve seen in *A*, under higher magnification, showing cocci, cocci in small chains, coccobacilli and rods (hematoxylin and eosin stain; × 950).

G, pleural exudate of a rat inoculated with a culture of Actinomyces from the involved mitral valve (hematoxylin and eosin stain; × 75). See also figure 5 *C*.

mentioned basophilic clumps and clusters to consist of basophilic cocci, diplococci, streptococci, rods, occasional clavate forms and short filaments, an occasional one of which showed small branches. This branching form was infrequent and difficult to demonstrate. Some of the rods were beaded and assumed the appearance of diphtheroids.. Others stained solidly. A few showed bipolar staining. Many of the rods were small and appeared similar to coccobacilli in structure. The predominating structures were the rods and the coccobacillary forms. Gram's stain showed the structures described as micro-organisms to be gram-variable. This stain showed that some of the rods were gram-negative with gram-positive poles.

Section of the myocardium showed areas of mild focal inflammatory reaction in the connective tissue stroma, observed by the presence of predominantly polymorphonuclear leukocytes and a few lymphocytes and macrophages, particularly in the perivascular areas. There was a moderate increase of epicardial fat. The arteries showed mild to moderate thickening of the intima. Section of a papillary muscle showed focal areas of microscopic abscesses in the connective tissue stroma (fig. 2*B*).

(*c*) Spleen (fig. 3*B*): A section of the spleen stained with hematoxylin and eosin showed an old infarct, evidenced by the ghostlike appearance of the entire section, which revealed indistinctness of outline of the entire splenic structure associated with old areas of hemorrhage and necrosis. In these areas an indistinct appearance of trabeculae, central arteries, veins and red and white pulp was noted. The white pulp was markedly decreased, and none of the scattered lymphoid nodule-like structures showed germinal centers. Some of the central arteries were completely occluded by basophilic clumps of cocci, rods, and short and thin filaments in an amorphous eosinophilic substance. Many of the perivascular areas were diffusely infiltrated, predominantly by degenerated polymorphonuclear leukocytes. Several of these cells extended into the adjacent pulp for a variable distance. The capsule showed loss of distinctness of outline to a variable degree.

(*d*) Liver (fig. 3*C*): A section stained with hematoxylin and eosin showed a moderate increase of lymphocytic infiltration in the portal areas. The sinusoids were dilated, and many of them were mildly infiltrated, by polymorphonuclear leukocytes and a few lymphocytes, extending through the lobules. Occasional microscopic abscesses were present in the central areas of the lobules.

(*e*) Intestine (fig. 3*D*): A section stained with hematoxylin and eosin showed extensive areas of necrosis, hemorrhage and abscess formation through all layers of the segment of small intestine. Some segments were entirely denuded of mucosal surface. Some of the blood vessels showed necrotic walls and an eosinophilic and hyalinized content within their lumens, associated with cellular debris, which occluded some of the lumens. Other lumens seemed almost occluded by basophilic clumps of cocci, streptococci and rods, already described. These structures were also seen in clumps in the eosinophilic masses among the numerous polymorphonulear leukocytes in the adjacent abscess.

(*f*) Kidneys (fig. 3*E*): A section stained with hematoxylin and eosin showed degenerative changes in several glomeruli, observed in the hyalinization of a variable portion of the glomerular tuft, particularly at the base. Some of Bowman's capsules showed mild inclusions of polymorphonuclear leukocytes. Some of the lumens of the tubules showed inclusions of macrophages laden with a deep yellow pigment. Many of the collecting tubules contained numerous erythrocytes. There were focal and mildly diffuse inflammatory changes in the parenchyma with presence of predominant polymorphonuclear leukocytes and fewer lymphocytes, macrophages and plasma cells. Many small parenchymal hemorrhages were present. An infarct of moderate size was also seen. A small area showed pyelone-

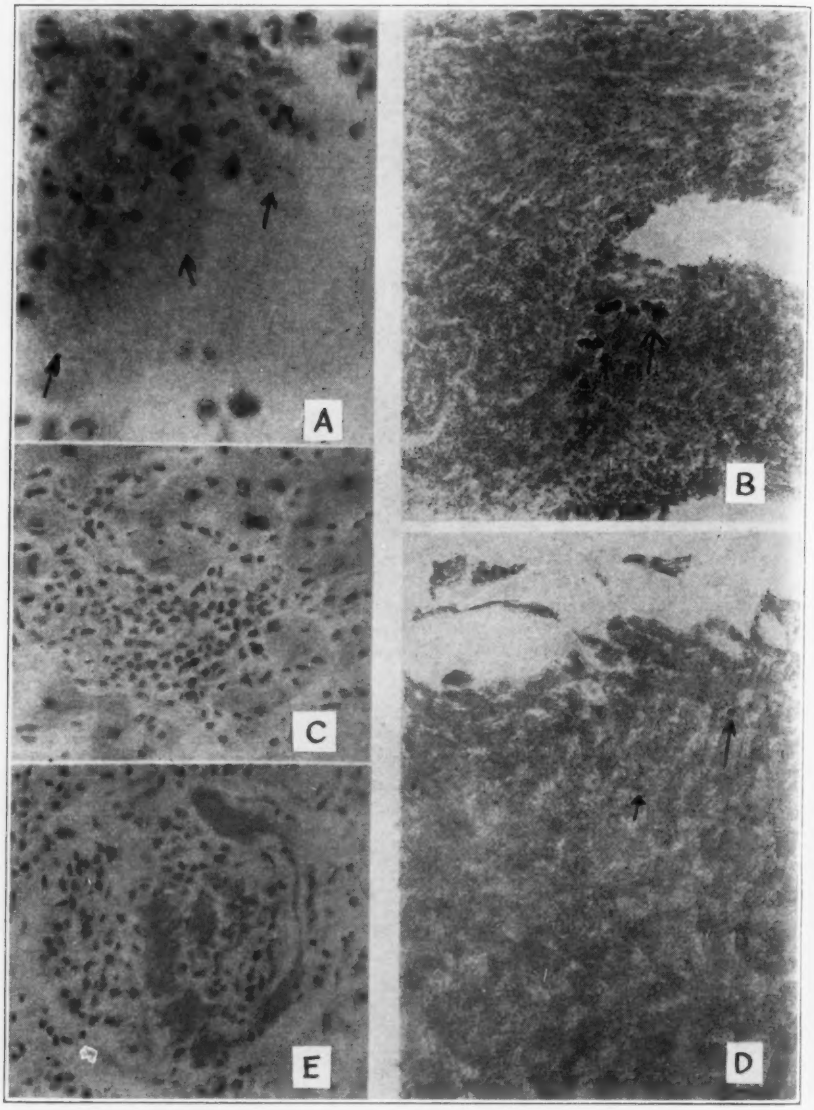

Fig. 3 (case 1).—*A*, higher magnification of figure 2 *G*, showing cocci and rods (hematoxylin and eosin stain; × 950).

B, spleen showing occluded blood vessels (hematoxylin and eosin stain; × 100).

C, liver showing a microscopic abscess (hematoxylin and eosin stain; × 400).

D, small intestine showing necrosis of tissue and occluded vascular lumens (hematoxylin and eosin stain; × 75).

E, renal glomerulus showing degenerative changes (hematoxylin and eosin stain; × 400).

phritic changes, evidenced by areas of hyalinization together with mild lymphocytic infiltration in the connective tissue stroma.

Cultures of the Mitral Valve.—A large segment of the growth of the mitral valve was washed several times in sterile isotonic solution of sodium chloride. It was then placed in a sterile Petri dish and seared over the entire external surface with a red hot spatula. At this stage it was removed to a second sterile Petri dish, where the seared tissue was cut with a sterile scalpel. Fragments from the inner surfaces of the cut tissue were cultured aerobically, under reduced oxygen tension and under carbon dioxide tension, on several blood slants (10 and 33 per cent whole blood with 2 per cent dextrose agar base), on dextrose agar slants, on plain agar and in "hormone" broth,[5a] all at 37 C. All inoculated mediums left in the incubator aerobically and under reduced oxygen tension remained sterile. Only the blood slants and the "hormone" broth incubated under carbon dioxide tension showed growth. This growth was slow. Cultures were studied from growth of single colonies. The blood slants showed small pinpoint colonies in five days. These were gray-brown, soft in consistency and easily removed from the slant. Subsequently, the colonies became somewhat larger, their diameter increasing to as much as 0.2 cm. The color remained the same, but the consistency became firmer. Transfers were made every week. After thirty-five days the colonies had died; further subcultures showed no growth.

In "hormone" broth, small soft gray granule-like colonies were visible in a week. These were transferred to blood plates and developed the characteristics described in the foregoing paragraph. Colonies transferred from blood plates to dextrose agar grew with difficulty under carbon dioxide tension.

Microscopically, the five days' cultural growth (fig. 4 *E*) showed gram-variable cocci, diplococci, streptococci, rods and diplobacilli of variable size and shapes. On dextrose agar a fourteen day old growth showed gram-variable cocci and rods, some of which measured up to about 0.7 micron in width. Some rods were long and straight; others were clavate. These structures took a basophilic stain with Giemsa's method. On blood slants the sixteen day old growth (figs. 4 *F, G* and I) showed gram-variable cocci, diplococci, streptococci, rods and a few filaments, some of which showed septums and occasional ones branching forms. The predominating form was the rod. These structures took a basophilic stain with Giemsa's method. Many of these rods presented a morphologic similarity to those observed in the tissue section of the mitral valve. The twenty-six day old growth showed cocci, diplococci, streptococci, rods, diplobacilli, beaded rods, clavate forms and filaments, some of which showed septums and a few of which showed short rami. Occasional forms showed delicate mycelia, with septums and rami, extending from an oval body (fig. 4 *H*). These filaments measured up to about 0.5 micron in width. The hematoxylin and eosin stain showed these structures to be both basophilic and eosinophilic. The twenty-eight days' growth showed several branching filaments in the direct unstained preparation in isotonic solution of sodium

5a. "Hormone" broth is made up as follows: Step 1. Add lean ground beef or veal, 500 Gm., to distilled water, 1,000 cc., and heat until mixture just begins to boil; then place in bath at 56 C. for one hour, after which filter the mixture through gauze and a thin layer of cotton. (The filtering through gauze and cotton permits enrichment of the medium.)

Step 2. Add: proteose peptone, 10 Gm., sodium chloride, 5 Gm.; disodium phosphate, 2 Gm.; sodium citrate, 2 Gm.; Bacto-dextrose, 1 Gm.; agar, 1.5 Gm.; Bacto-gelatin, 10 Gm. Mix and heat until agar dissolves. (Do not allow it to boil more than thirty-seconds.) Restore volume to 1,000 cc. Titrate to p_H 7.4. Bottle and sterilize at 15 pounds (6.5 Kg.) for twenty minutes.

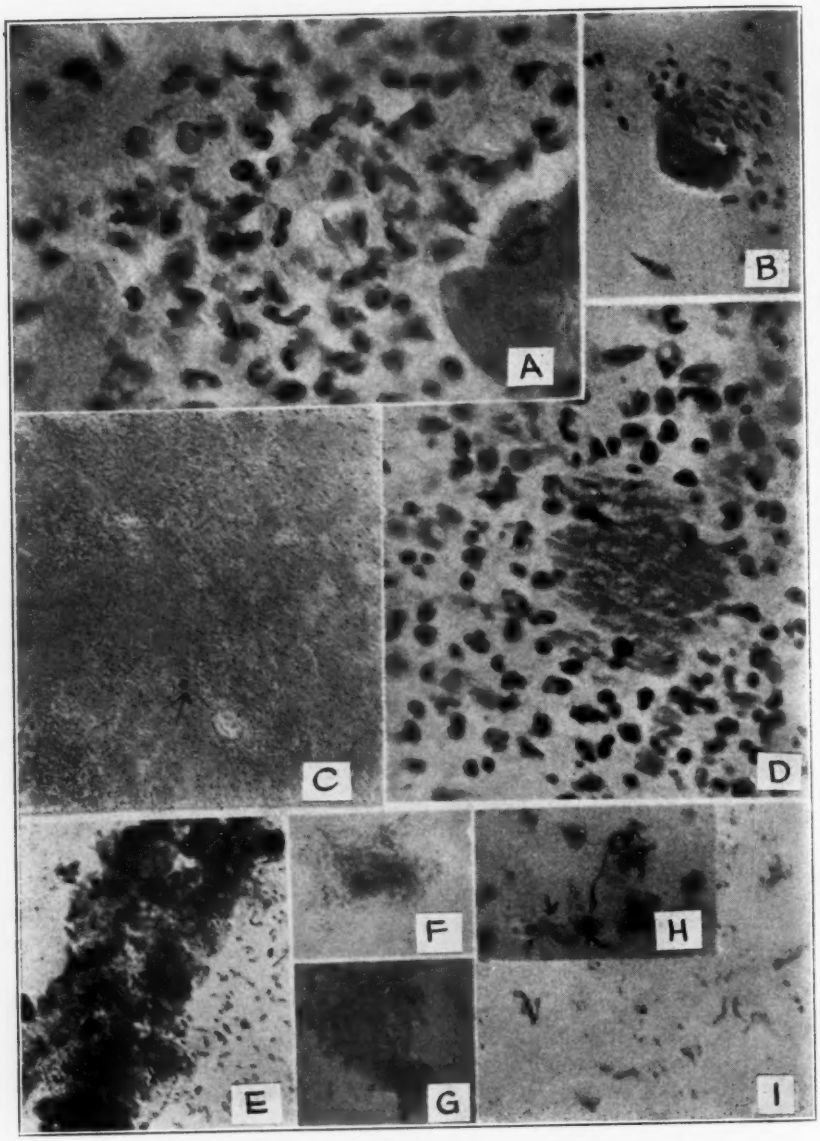

Figure 4

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chloride (fig. 5 *A*). The hematoxylin and eosin stain of the thirty-three days' growth showed degenerated eosinophilic rods and a few basophilic filaments. An occasional basophilic filament showed septums, fusiform enlargement and a chlamydospore (fig. 5 *B*).

Animal Inoculation in Case 1.—On April 5, 1944 a white rat was inoculated intraperitoneally with an eight days' growth from a culture of the vegetation of the mitral valve on a blood slant. The rat died July 8, ninety-four days after inoculation, and autopsy was performed shortly after death, according to the technic described subsequently. The animal was emaciated. There were extensive pathologic changes in both lungs, with marked fibrinous exudation (fig. 1 *C*) over pleural surfaces bilaterally. Both the lungs and the mediastinum showed multiple abscesses with a glairy and mucoid exudation of a green-yellow color. Other abscesses showed a finely granular substance, but no true sulfur granules were present. The upper lobe of the right lung showed a finely granular structure of firm consistency and a gray-red color. A mesenteric nodule (fig. 1 *B*), measuring about 2 cm. at the largest dimension, was smooth, firm and of a gray color. On sectioning, the surfaces showed a hemorrhagic spot measuring up to about 0.6 cm. at the largest dimension. The remaining portions of the surfaces made by sectioning were mottled with gray and red-brown colors.

Microscopic Observations.—(*a*) Lung: Sections stained with hematoxylin and eosin showed chronic peribronchial and peribronchiolar inflammatory changes. There were also focal areas of bronchopneumonia, atelectasis, congestion and hemorrhage. One arteriole in particular showed splitting of the internal and the external elastic lamella and marked thickening of the media with zones of fatty ingrowth. Adjacent to the external elastic lamella were eosinophilic zones of hyalinization.

Pleural surfaces showed extensive acute purulent inflammatory changes (figs. 2 *G* and 5 *C*), evidenced by diffuse cellular infiltration, predominantly polymorphonuclear leukocytes, with several lymphocytes and some macrophages. Many of these cells showed necrosis. Fibrous strands of eosinophilic staining were present among these cells in various areas. Numerous basophilic cocci, cocci in chains and a few rods and diplobacilli were scattered among the inflammatory cells. Some of the described inflammatory cells extended into the adjacent pulmonary parenchyma. Many of the described micro-organisms (fig. 3 *A*) showed

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Explanation of Plate.

Fig. 4 (case 1).—*A*, kidney showing interstitial inflammatory reaction (hematoxylin and eosin stain; × 950).

B, brain showing blood vessel occluded by micro-organisms and perivascular inflammation (hematoxylin and eosin stain; × 400).

C, brain showing a focus of micro-organisms circumscribed by inflammatory cells (hematoxylin and eosin stain; × 950).

D, brain showing a focus of micro-organisms (hematoxylin and eosin stain; × 75).

E, culture of the involved mitral valve showing five day old growth (Gram's stain; × 950).

F, *G* and *I*, culture of the mitral valve showing variations of forms in a sixteen day old growth (Giemsa's stain; × 950).

H, culture of the mitral valve showing a branching form in a twenty-six day old growth (hematoxylin and eosin stain; × 950).

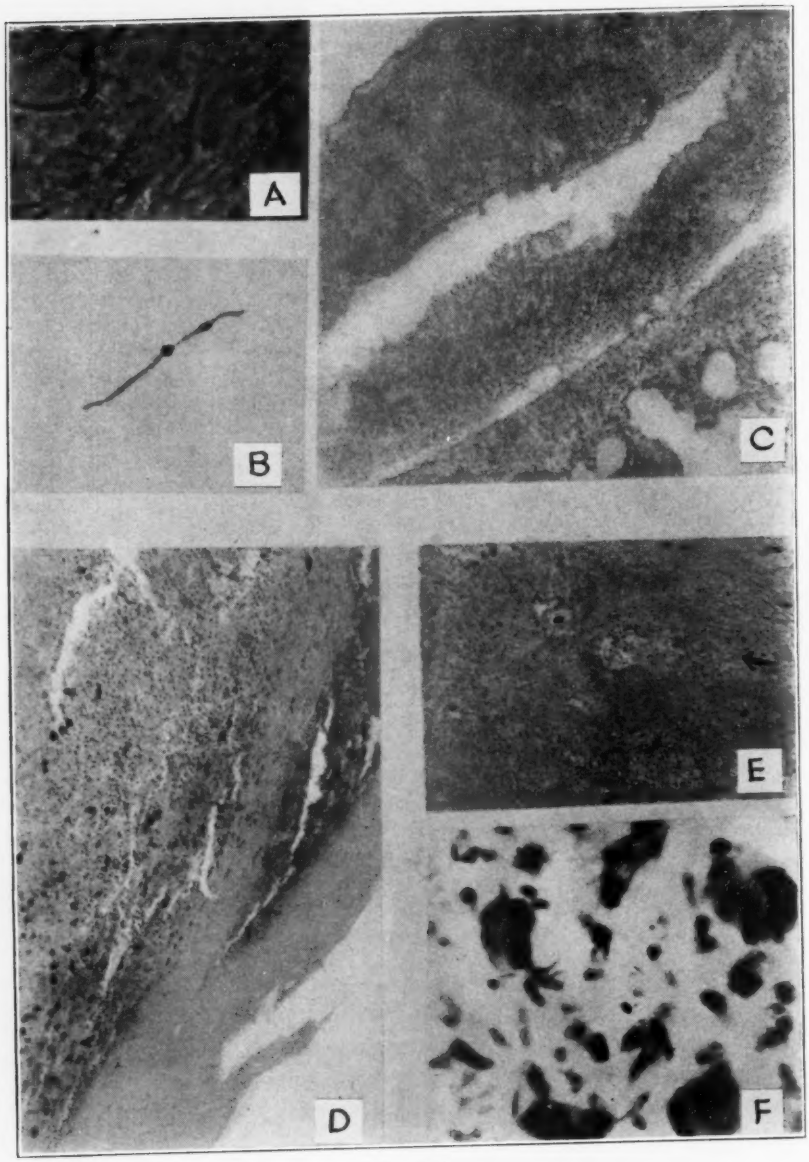

Figure 5

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morphologic and staining characteristics similar to those observed in the heart valve of the patient. Occasional basophilic clumps of cocci and cocci in chains were present among the inflammatory cells in the pulmonary parenchyma.

(*b*) Lymph Node: A section (fig. 5 *D*) taken from the node already described in the gross and stained with hematoxylin and eosin showed areas of necrosis involving large segments of the capsule and extending for a short distance in the adjacent parenchyma, illustrated by the ghostlike appearance of these structures. Other segments of the capsule and large areas of the node showed only mild loss of distinctness of outline of cellular detail. The capsule was thickened. The subcapsular sinus was not recognized. The detailed normal structure of the lymph node had been lost. Focal areas of lymphocytic aggregation were present about the peripheral portion of the node, and fewer of these showed portions of recognizable germinal centers. Extensive areas of hemorrhage were present in the node. Connective tissue trabeculae were recognized as extending from the capsule. There were extensive and diffuse infiltrations of large round and polyhedral mononuclear cells with basophilic round vesicular nuclei, centrally and eccentrically located. Some large cells had two nuclei, and others had several. There were some areas diffusely infiltrated by similar cells associated with several polymorphonuclear leukocytes. This combination of cells was not predominant, however. Some areas showed marked fibroblastic proliferation, particularly in the perivascular areas, in which regions some basophilic rods and diplobacillary forms were present (fig. 6 *A*, *B* and *C*). Other areas showed fibroblastic proliferation in a loose connective tissue stroma associated with an amorphous eosinophilic coagulum and scattered macrophages and lymphocytes. Some of the vessels showed mild intimal thickening and narrowing of their lumens. In addition to the aforementioned findings, there were numerous crystals (fig. 5 *F*) of rectangular, square and slightly fusiform shapes and of eosinophilic staining. Some of these crystals were homogeneous and others appeared longitudinally striated. Some were extracellular, and others were within the cytoplasm of the large mononuclear cells. These crystals at times assumed the shape of portions of an asteroid, but true asteroids were not found. The crystals were gram-variable with MacCallum's modification of the Gram stain. The entire picture of the lymph node was consistent with a process of chronic inflammation and lymphoid hyperplasia with subsequent pressure necrosis of tissue due to impairment of blood supply. Particular attention should be given to the description of the bacillary structures in the node, since similar

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EXPLANATION OF PLATE.

Fig. 5 (case 1).—*A*, culture of the mitral valve showing branching filamentous forms in twenty-eight day old growth (direct and unstained preparation; × 950).

B, culture of the mitral valve showing a chlamydospore in a thirty-three day old growth (hematoxylin and eosin stain; × 950).

C, lung and pleural surface of a rat inoculated with a culture of the mitral valve (hematoxylin and eosin stain; × 75). See also figures 2 *G* and 3 *A*.

D, lymph node of a rat inoculated with a culture of the mitral valve (hematoxylin and eosin stain; × 75). See also figure 1 *B*.

E, same as *D*. The arrow points to the locality of the rod structures indicated in figure 6 *A*, *B*, and *C*.

F, crystals observed in the lymph node shown in *D* (Gram's stain, MacCallum's modification of Goodpasture's method; × 950).

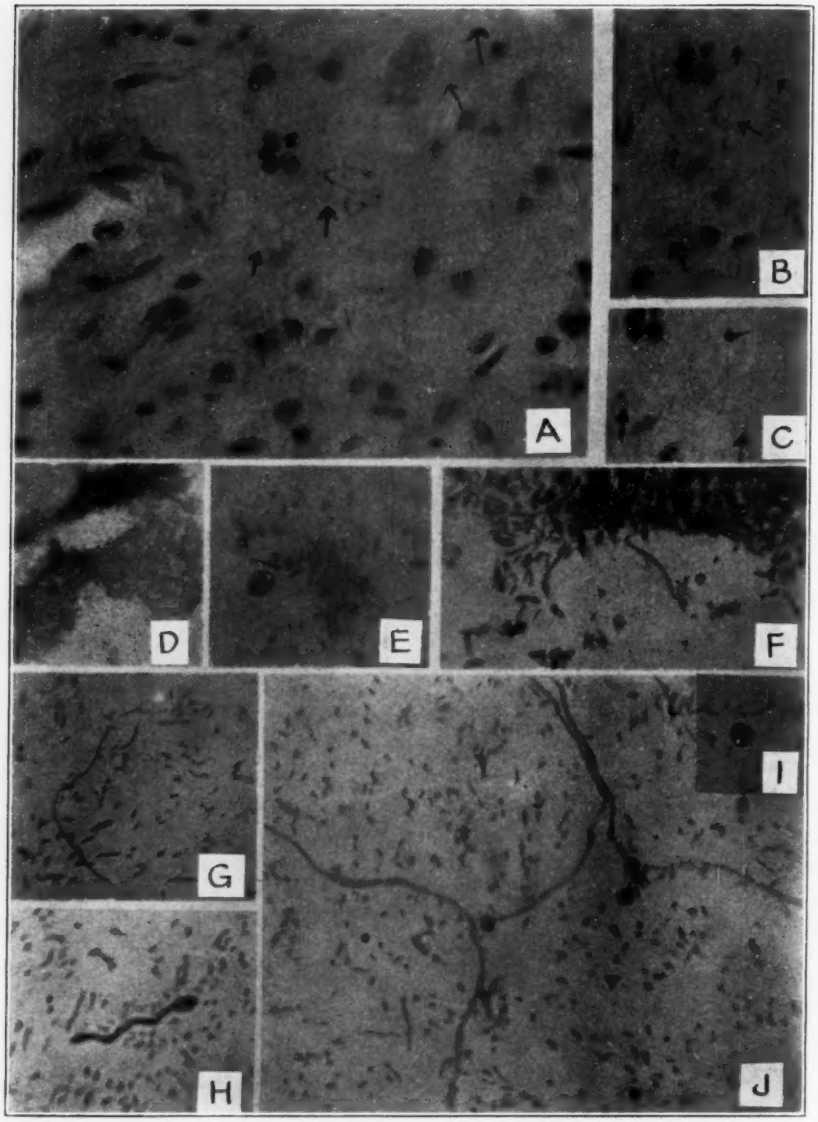

Fig. 6 (case 1).—*A*, *B* and *C*, lymph node shown in figure 5 *E*. Arrows point to bacillary structures in the fibrous connective tissue stroma of the perivascular area (hematoxylin and eosin stain; × 950).

D, *E*, *F* and *G*, coccal, bacillary and filamentous forms as seen in seventy-two hours' growth of cultures of pulmonary abscesses and pleural exudate of a rat inoculated with a culture of the mitral valve (Gram's stain; × 950).

H, *I* and *J*, twenty-one days' cultural growth of the micro-organism in *D* (Gram's stain; × 950).

structures were seen in a lymph node (fig. 1 *D*) from another rat inoculated with cultures from true "sulfur granules" of another patient.[6]

Culture from Inoculated Animal.[7]—The rat was immersed in solution of formaldehyde U.S.P. diluted 1:10, to kill external contaminants. The body cavities of the animal were opened with an aseptic technic. Pulmonary abscesses and pleural exudate of the rat were cultured in the manner described on page 215 under "Cultures of the Mitral Valve." In gross appearance the colonies were similar to those isolated from the patient's heart valve, but they developed more rapidly. In three days they were of about the same size as those observed at five days in cultures of the patient's mitral valve. These organisms, like those of the patient's heart valve, grew only under carbon dioxide tension.

Microscopically, the seventy-two hour growth showed gram-variable cocci, diplococci, rods and some filaments (fig. 6 *D, E, F* and *G*), some which showed septums. Occasional branching forms were present. A few round and baglike structures (fig. 6 *I*), measuring from about 3 to 4 microns in diameter, were also seen. These bags contained numerous small granules, and they will be mentioned again in connection with other strains of Actinomyces in another paper.[6] Some of the rods present resembled diphtheroids. The twenty-one day cultural growth showed gram-variable rods and filaments, some of which had septums and branching forms. Filaments sprouting from oval bodies (fig. 6 *H*) and chlamydospores (fig. 6 *J*) were present in this culture. The round bags aforementioned were also present. Transfers from this stage showed no growth.

Case 2.—This case came to my attention while the preparation of this paper was in progress.

Clinical History.—A 71 year old Jamaican Negro woman, a housewife, died in Panama City, Republic of Panama, Nov. 17, 1945. The body was brought to the Board of Health Laboratory, Ançon, Canal Zone. A death certificate accompanying the body gave the cause as "cardiorenal" disease. The attending physician informed me that he had seen the patient off and on for several years and that during this time she had presented the syndrome of typical hypertensive heart disease with damage of the kidneys. She had high blood pressure and presented evidence of cardiac decompensation on occasions. She had never shown, to his knowledge, any evidence of rheumatic heart disease or any symptoms of subacute bacterial endocarditis. No petechiae had been found. The husband said she had been confined to bed at home for the last two months before her death.

Autopsy.—The heart was enlarged and weighed 470 Gm. There was particularly evident prepondérance of the left ventricle. The pericardial sac contained 30 cc. of straw-colored fluid. The endocardium of the left auricle was wrinkled in various areas. Fine fibrotic nodules were present in the aortic and the mitral

6. Wedding, E. S.: Actinomycosis of the Central Nervous System and Its Coverings, Primary and Secondary Forms: Report of Seven Cases and Review of Literature, unpublished data.

7. A culture of the micro-organism isolated from this animal was inoculated into a second rat, which was killed eighteen months after inoculation. Although the later rat looked entirely healthy prior to death, it presented several large mesenteric lymph nodes quite similar in their gross and microscopic pathologic aspects to the lymph node described in the first rat except for the absence of any forms of the micro-organism and crystals in histologic preparations.

leaflets, consistent with inactive rheumatic heart disease. The nodules of the aortic cusps presented superficial growths of a verrucous structure, which were friable. The left aortic leaflet was ruptured. The right posterior aortic leaflet was bound to the anterior one. An area of fibrosis was evident in the endocardium of the left ventricle.

Microscopic examination of a section of the aortic valve, taken through a region of the verrucous growth, showed diffuse acute inflammatory changes through the greater portion of the section, indicated by the cellular infiltration, predominantly polymorphonuclear leukocytes with a few lymphocytes and macrophages. In various areas, diffuse fibroblastic proliferation was present, particularly toward the base. Regions of the valvular border showed breaks in continuity of outline. These regions were associated with the inflammatory cells described, which covered the adjacent borders and were in line of direct contact with the inflammatory cells which extended throughout the entire thickness of the section. At the base the inflammatory cells extended into the adjacent fibrous connective tissue stroma supporting the myocardial fasciculi. Various areas adjacent to the border showed necrosis of tissue. Focal areas of calcific changes were present in the border of the valve, near some of which focal collections of basophilic structures were observed, with the oil immersion objective of the microscope, to consist of basophilic cocci, coccobacilli, rods and long, thin filaments. Some of these structures stained lightly, and others stained deeply. Adjacent regions were diffusely infiltrated by basophilic cocci, coccobacilli, rods and a few short filaments among the inflammatory cells. Some of the filaments were septate, revealed by Gram's stain. This stain showed structures similar to those described to be gram-positive. Clavate forms were also present. A few of the rods were gram-negative.

A direct smear prepared from the vegetations of the valve and stained by Gram's method showed structures the same as those already described except that no branching forms were observed.

Cultures were made from the cardiac vegetations, and an aerobic strain of Actinomyces was recovered in twenty-four hours, in which stage the structures occurred as cocci, rods and filaments. The colonies were gray-white and showed branching filaments after eight days. These stained gram-variable. Unfortunately, an adequate bacteriologic technic was not carried out, and the organism was not recovered in pure culture from the start, although separate colonies of Actinomyces were singled out and grown in pure culture from this stage. No animals were inoculated.

Laboratory reports on an autopsy blood specimen showed 183.9 mg. of nonprotein nitrogen, 149.6 mg. of urea nitrogen, 12.5 mg. of creatinine and 30 mg. of glucose per hundred cubic centimeters. The Wassermann and the Kahn test of the blood were negative.

COMMENT

A vast amount of literature has been written on the subject of actinomycosis. Yet it is surprising how many physicians think of this diseasse in terms of the "sulfur granule" only. I believe that it is entirely proper to emphasize the established facts that the granule is not a true criterion for the diagnosis of actinomycosis, that other organisms may produce granules and that some species of Actinomyces do not form clubs. Numerous strains of Actinomyces have been reported, both

as pathogens and as saprophytes (Bergey [8]; Dodge [9]; Topley and Wilson [10]). Classifications have been discussed and disputed. Pathogens have been described as anaerobic, microaerophilic and aerobic. Some strains have been mentioned as acid fast. Emmons [11] has clarified and simplified the understanding of actinomycosis by defining the disease as "an infection caused by invasion of the host by some species of Actinomyces." He refers to Bergey and Topley and Wilson as authority for his usage. By keeping such a definition in mind and by understanding the pleomorphic cultural characteristics of Actinomyces, which occurs as cocci, rods, filaments, branching filaments, irregular vesicles and diphtheroid forms (Emmons [11]; Naeslund [12]; Kessel [13]; Negroni [14]) it is probable that greater care will be used in the laboratory to recover the organism. Such an organism recovered by competent personnel would then be less apt to be considered a contaminant and discarded on this ground, which would be the easiest way out of doing a job.

It is of interest to read how Naeslund [12] referred to the pleomorphism: "There are hardly any known bacteria that exhibit such large variations from a cultural point of view as Actinomyces." Novak and Henrici,[15] and Sartory and Meyer [16] made references to a filtrable form of Actinomyces. I [6] have recovered a filtrable form repeatedly in cultures of one of my strains of Actinomyces.

In this paper the emphasis of the review of the literature has been confined to those cases in which evidence of endocarditis was presented without any evidence of a portal of entry. The organism reported by Jervell was classified as a leptothrix by him, and it is not to be considered as a strain of Actinomyces. The organism recovered from the blood stream in the first case of Alestra and Girolami developed into

8. Bergey, D. H.: Bergey's Manual of Determinative Bacteriology, ed. 5, Baltimore, Williams & Wilkins Company, 1939, p. 839.

9. Dodge, C. W.: Medical Mycology, St. Louis, C. V. Mosby Company, 1935, p. 705.

10. Topley, W. W. C., and Wilson, G. S.: Principles of Bacteriology and Immunity, ed. 2, Baltimore, William Wood & Company, 1937, p. 263.

11. Emmons, C. W.: Actinomyces and Actinomycosis, Puerto Rico J. Pub. Health & Trop. Med. **11**:63-76, 1935.

12. Naeslund, C.: Studies of Actinomyces from the Oral Cavity, Acta path. et microbiol. Scandinav. **2**:110-140, 1925.

13. Kessel, J. F., and Goolden, E. B.: A Comparison of Strains of Actinomyces Recovered from Human Lesions, Am. J. Trop. Med. **18**:689-701, 1938.

14. Negroni, P.: Actinomicosis humanas producidas por agentes anaerobios, Rev. argent. de dermatosif. **18**:24-27, 1934.

15. Novak, M. V., and Henrici, A. T.: Pleomorphic Organisms Showing Relationships Between Staphylococci and Actinomycetes, J. Infect. Dis. **52**:253-267, 1933.

16. Sartory, A.; Sartory, R., and Meyer, J.: Sur les propriétés ultrafiltrantes de l' "Actinomyces bovis" Harz à travers les sacs de collodion implantés dans le péritoine du cobaye, Bull. Acad. de méd., Paris **110**:797-798, 1933.

filaments, but no branched forms occurred. Since the authors reported that the strain was lost in an early stage of development, it is not possible to classify it either as a leptothrix or as strain of Actinomyces. The strain recovered from the blood stream in the second case developed into filaments, but branching forms are not mentioned. For this reason, it cannot be regarded as a species of Actinomyces, although the authors believed they were dealing with "Nocardia." Cornell and Shookhoff [1] referred to the case of Lutz (table 3) with regard to a primary cardiac involvement with multiple small abscesses in the wall of the right ventricle, but the details are not complete. The organism described by Basu [5] developed branching forms, but the author does not mention cardiac involvement. Carrión [17] reported the recovery of positive rods and branching filaments from a blood culture in case 2, but there is no reference to cardiac lesions. Freed [18] reported blood cultures positive for Actinomyces, but there was no clinical evidence of cardiac impairment, although the endocardium of the right ventricle was perforated by the abscess. Bruun [19] referred to Schlegel's case of actinomycotic pyemia by extension to the veins from the intestines. No cardiac involvement was mentioned. Uhr [4] reported recovery of A. bovis, identified by cultural characteristics, from the blood stream and from vegetations on the mitral valve.

All in all, 4 cases have been reported in which symptoms of subacute endocarditis were considered to be due to higher forms of bacteria and in which there was no evidence as to the portal of entry. It is to be remembered that Uhr stated that his case was indistinguishable both clinically and pathologically from "an ordinary case of subacute bacterial endocarditis." Naeslund,[12] Emmons [20] (who also referred to the work of Lord and Wright) and others have shown the presence of Actinomyces in the flora of human mouths and tonsillar crypts. In reference to these findings, Carrión [17] stated that he thought it reasonable to expect a larger number of actinomycotic infections in human disease. It may possibly be that these sources serve as portals of entry.

In reference to inoculation of animals, Jervell, Uhr and Basu reported no success. Alestra and Girolami reported recovery of an organism in their case 2 from guinea pigs and rabbits which died twenty-four hours after inoculation. Gose [21] reported no success. Carrión reported no

17. Carrión, A. L.: Actinomycosis in Puerto Rico, Puerto Rico J. Pub. Health & Trop. Med. **13**:367-382, 1938.

18. Freed, D. F., and Light, F.: Generalized Actinomycosis with Positive Blood Cultures, Pennsylvania M. J. **36**:25-29, 1932.

19. Brunn, E.: Et tilfælde av aktinomykose pyæmi, Hospitalstid. **81**:16-20, 1938.

20. Emmons, C. W.: The Isolation of Actinomyces Bovis from Tonsillar Granules, Pub. Health Rep. **53**:1967-1975, 1938.

21. Gose, C. A.: A Case of Constrictive Pericarditis Due to Actinomycosis, Memphis M. J. **16**:56-58, 1942.

specific lesions. In a survey of the rest of the available literature I failed to find any reports of "takes" in animals, as the diagnosis was based on finding the granules in histologic sections or in the exudates in the cases of actinomycosis of the heart by secondary involvement from a distant primary focus. The literature is also scant in reference, to cultural findings in these cases. Tubbs and Turner [22] reported cultures of Streptothrix in typical A. bovis form from the sputum and from abscesses of the pericardial sac. Genthner and Pendleton [23] referred to Actinomyces cultured from the purulent pleural surface.

Direct smears or histologic sections prepared from cardiac and associated lesions which showed coccal or bacillary forms have been reported in a few cases. Paltauf,[24] as early as 1890, mentioned finding gram-positive coccal structures, small bent rods and branching filaments in the pus of the metastatic abscesses and in the branches of the pulmonary artery without finding the granules in these areas. Numerous granules, however, were present in the pus of the pericardial exudate. Paetzold [25] referred to Richter's case in which cocci in chains were observed. Jervell described gram-positive coccoid rods in the spleen and structures of the same type in the histologic section of the heart valve, where some of these structures occurred in chains. Uhr described a bacterial clump in an ateriole.

Although it is known that Actinomyces is pleomorphic, the conclusion cannot be drawn from smears or histologic sections alone that the coccal, bacillary and unbranched filamentous forms belong to the developing stages of Actinomyces unless cultures substantiate this. In regard to the second case reported in this paper it is quite reasonable to assume that these various forms belonged to the same strain of Actinomyces, because of the branching filamentous structures present and the coccal and bacillary forms diffusely spread out among the inflammatory cells, which is consistent with the picture of cellular response to infection rather than with that of contamination. Again, the clinical course was not that of an acute infection with a pyogenic bacterial organism. The cultural findings tie in with the foregoing description, although the organism was not recovered in pure culture at the first isolation.

The credit of originally suspecting the organism to be of the genus Actinomyces goes to Dr. W. K. Bell, the intern who made a smear of the vegetations of the heart valve and noticed the filaments. Although

22. Tubbs, O. S., and Turner, J. W. A.: Primary Actinomycosis of the Thorax, St. Barth. Hosp. J. **44**:184-188, 1937.

23. Genthner, W. M., and Pendleton, R. K.: Pulmonary Actinomycosis: A Report of Two Cases, New York State J. Med. **32**:1283-1287, 1932.

24. Paltauf, R.: Wien. klin. Wchnschr. **3**:487, 1890.

25. Paetzold, P.: Ein Fall von generalisierter Aktinomykose beim Menschen, Frankfurt. Ztschr. f. Path. **16**:415-440, 1914-1915.

definite and strict orders had been left with the department that all autopsied heart valves should be submitted to me, my attention was not called to the specimen until the following day. This is mentioned merely to indicate specifically how easily such an infection could be overlooked through inadequate observation or a slip in technical procedure. If this point is carried across, the laboratory mistake in this instance would be of considerable value. It is impossible to surmise how many cases may have been diagnosed as cases of subacute bacterial endocarditis by history and histologic sections alone in the absence of cultures, or in the presence of sterile cultures not kept sufficiently long or only aerobically, or in the presence of inadequately prepared cultures. Branching forms took sixteen days for recognition in the cultures of case 1, and chlamydospores were not observed before twenty-six days' growth of the culture of the heart valve. The presence of chlamydospores should not be alarming. They have been mentioned as occurring in strains of Actinomyces by Dodge,[9] and they have been observed in other strains by me.[6] It is not intended to convey the thought that cardiac actinomycosis will be found in great numbers of cases by improved technic and care, but it is certain that the results will at least be more reliable. To achieve this, it is just as important to scrutinize closely the structures of the organism in tissue sections with the oil immersion objective of the microscope.

From the animal experimentation in case 1 attention is called to the coccal and bacillary forms in tissues of the rat. No filaments were found in these tissues, whereas in cultures of the organism filaments and chlamydospores developed. The similarity of microscopic changes in tissues of animals inoculated with cultures of a strain of A. bovis is discussed in another paper.[6]

Pathologic involvement of lymph nodes associated with cardiac actinomycosis is mentioned by Ruhräh,[26] Kissling[27] (*Die obduktion ergab Mediastinitis und Lymphadenitis actinomycotica mit Durchbruch in die Vena cava super* [The autopsy disclosed actinomycotic mediastinitis and lymphadenitis with a break-through into the vena cava superior]), Werthemann.[28] Gose[21] and Cornell and Shookhoff.[1] The picture of the pathologic changes varied from one that was nonspecific to that described by Kissling. I[6] have recovered strains of Actinomyces[29] from cultures of specimens of spinal fluid and of pus of brain

26. Ruhräh, J.: Actinomycosis in Man, Ann. Surg. **30**:438-440, 1899.

27. Kissling: Biologische Abteilung des ärztlichen Vereins in Hamburg, München. med. Wchnschr. **56**:207-208, 1909.

28. Werthemann, H.: Ueber die Generalisation der Aktinomykose, Virchows Arch. f. path. Anat. **255**:734, 1925.

29. Harley, R. D., and Wedding, E. S.: Syndrome of Uveitis, Meningo-Encephalitis, Alopecia, Poliosis, and Dysacousia: Report of a Case Due to Actinomyces, to be published.

abscesses showing rods bearing a morphologic resemblance to those observed in the lymph node of the rat inoculated in case 1.

The clinical course in case 1 simulated that of rheumatic endocarditis for some time, but the type of fever curve was recognized as unusual. The rises of temperature responded for over fifteen months to sulfonamide drugs. The clinical picture was considered that of subacute endocarditis.

The clinical course in case 2 was that of typical hypertensive cardiovascular disease, with decompensation, terminal renal damage and azotemia. Any evidence of subacute endocarditis was not recognized by the attending physician. That this condition was present and active was illustrated by the histologic picture of the valve section from autopsy. However, the predominant findings from the first-mentioned condition, together with the physiologic effects produced by a ruptured aortic cusp, may have masked any symptoms of the subacute endocarditis present. How long the subacute endocarditis had been present is difficult to estimate. Certainly, it was not the cause of death in this case. Evidence of inactive rheumatic heart disease was present.

SUMMARY

A review of literature disclosed reports of 4 cases in which there was a clinical picture of subacute bacterial endocarditis due to the higher forms of bacteria without any evidence of a portal of entry.

Of the 2 cases of actinomycotic endocarditis reported in this paper, one was characterized by the clinical picture of subacute endocarditis. The other case was not recognized before autopsy. The patient died of hypertensive heart disease with renal failure and azotemia. Evidence consistent with inactive rheumatic heart disease was present.

In case 1, inoculation of a rat produced pathologic evidence of infection with Actinomyces, and the organism was recovered in pure culture from the inoculated animal. Coccal structures, rods, filaments and branching filaments were observed in vegetations of the aortic valve in case 2. An aerobic strain of Actinomyces was recovered from the valve, but contaminants were present in the original culture. Nevertheless, the smears, the histologic sections and the cultures, together with the clinical history of the case, have been considered as supplying adequate evidence for a diagnosis of actinomycotic endocarditis.

It is important in such cases that laboratory procedures and technic be carried through completely, exactly and carefully, to exclude sources of error that may lead to failure of recognizing actinomycotic infections. A review of the literature shows that there is ample room for improvement in this respect.

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CARDIAC MANIFESTATIONS OF TOXIC ACTION OF EMETINE HYDROCHLORIDE IN AMEBIC DYSENTERY

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THE TOXIC action of emetine hydrochloride on the cardiovascular and neuromuscular systems has been well known for many years. In 1916 Levy and Rowntree [1] demonstrated by means of the electrocardiograph that an overdose of emetine hydrochloride in rabbits caused death by ventricular fibrillation. More recently Boyd and Scherf [2] observed intraventricular block, inversion of T waves and cardiac arrhythmias in experimental intoxication with emetine hydrochloride in cats.

In human beings the toxic effects of emetine hydrochloride on the neuromuscular system have been described more frequently than the cardiac manifestations. These consist principally in generalized muscular weakness, tremors and peripheral neuritis. Diarrhea, which may be bloody in severe conditions, vomiting and abdominal cramping pains are among the other commoner evidences of toxicity of emetine hydrochloride.

Although it has been well established that the long-continued administration of emetine hydrochloride in large doses in human beings will generally result in the development of signs of toxicity, it has not been sufficiently emphasized that the usual therapeutic dose may also produce serious injury. The great majority of reported fatalities in human beings have resulted from the administration of 20 grains (1.29 Gm.) or more, but six deaths have been reported after a total of only 10 grains (0.65 Gm.).[3] Furthermore, it has been pointed out[4] that the margin of safety between the effective and the toxic dose of emetine

1. Levy, R. L., and Rowntree, L.: On the Toxicity of Various Commercial Preparations of Emetine Hydrochloride, Arch. Int. Med. **17**:420 (March) 1916.

2. Boyd, L. J., and Scherf, D.: The Electrocardiogram in Acute Emetine Intoxication, J. Pharmacol. & Exper. Therap. **71**:362, 1941.

3. Heilig, R., and Visveswar, S. K.: On the Cardiac Effects of Emetine, Indian M. Gaz. **78**:419, 1943; abstracted, Trop. Dis. Bull. **41**:285, 1944.

4. Sollmann, T. H.: A Manual of Pharmacology and Its Application to Therapeutics and Toxicology, Philadelphia, W. B. Saunders Company, 1942.

hydrochloride is small. This has been partially attributed to the cumulative action of emetine hydrochloride resulting from its slow excretion through the kidneys and the intestinal tract.

Recent reports of the clinical effects of administration of emetine hydrochloride in several large series of cases have tended to minimize the risks of toxic reactions. In 1935 Brown [5] reported that of 554 patients with amebic dysentery treated with emetine hydrochloride toxic reactions, principally peripheral neuritis, developed in only 23. There were reactions in only 3 of those treated with 10 grains (0.65 Gm.) or less. In addition, he found only thirty-seven reported instances of toxicity of emetine hydrochloride in the literature prior to 1935, with ten deaths. Similarly, Heilig and Visveswar [3] failed to observe any significant alteration in the electrocardiogram, blood pressure or orthodiagram of 14 patients treated with twelve intramuscular injections of 1 grain (0.06 Gm.) of emetine hydrochloride daily. In a series of 72 patients treated by Hardgrove and Smith [6] in the Panama Canal Zone, only one serious cardiac effect, resembling cardiac infarction, was observed after ten intramuscular injections of 1 grain daily. Electrocardiographic changes developed in 53 per cent of the patients, the vast majority affecting the T waves; actual inversion of the T waves occurred in only 13 per cent. Hardgrove and Smith concluded that emetine hydrochloride in therapeutic doses produces only minor and transient electrocardiographic changes and that there is little risk involved in the use of emetine hydrochloride if electrocardiograms are taken during the course of treatment and the patient is kept in bed.

We have recently had the opportunity to observe 9 patients in whom toxic cardiac effects developed after the administration of emetine hydrochloride for amebic dysentery. These are reported in detail in order to reemphasize the possible danger in the administration of emetine hydrochloride and the precautions necessary during treatment.

MATERIAL

In November and December 1944 there were 21 patients recently treated with emetine hydrochloride for amebiasis in other medical installations who came under our observation. Only 4 of these patients had had electrocardiograms during the course of emetine hydrochloride therapy. Electrocardiograms were obtained on all patients on their admission to the hospital, and 8 of the 21 patients were found to have a distinctly abnormal record. Two of the patients had electrocardiograms that were considered borderline, and in the remainder no abnormali-

5. Brown, P. W.: Results and Dangers in the Treatment of Amebiasis: A Summary of Fifteen Years' Clinical Experience at the Mayo Clinic, J. A. M. A. **105**:1319 (Oct. 26) 1935.

6. Hardgrove, M., and Smith, E. R.: Effects of Emetine on the Electrocardiogram, Am. Heart J. **28**:752, 1944.

ties were found. Serial records at intervals of one to two weeks were obtained in the first two groups. An additional patient, admitted to our hospital at a later date, demonstrated toxic myocardial changes due to emetine hydrochloride and is included in this series. Three of the patients in the first group manifested obvious neuromuscular symptoms and signs, cramping abdominal pains and diarrhea that could be ascribed to toxicity of emetine hydrochloride. This report is based on a study of these 9 cases. The outstanding clinical features are listed in the table.

SUMMARY OF FINDINGS

Dose of Emetine.—The total dose of emetine hydrochloride administered prior to admission of the patients to the hospital ranged from 7 to 22 grains (0.45 to 1.42 Gm.). One patient (case 9) showed electrocardiographic changes after the administration of only 4 grains (0.26 Gm.) and received a total of 7 grains (0.45 Gm.). Two patients received a course of ten daily injections of 1 grain (0.06 Gm.) of emetine hydrochloride. Four patients received a total of 14 grains (0.91 Gm.), 2 in consecutive daily injections and 2 with a rest period of seven and ten days following the tenth injection. One patient had received 19 grains (1.25 Gm.) with a twelve day rest period following the fifth injection, and 1 patient had received a total of 22 grains (1.42 Gm.) administered in three courses over a period of thirty-four days.

Time of Appearance of Toxic Signs.—Whereas the neuromuscular manifestations of toxicity usually appeared during the period of administration of emetine hydrochloride, the time of the appearance of the abnormal electrocardiographic changes was difficult to ascertain. Control electrocardiograms were available in only 4 instances. In case 9, changes were noted after administration of only 4 grains (0.26 Gm.). In case 6, normal records were obtained after 6 and 12 grains (0.39 and 0.78 Gm.) were given, and an abnormal electrocardiogram was not demonstrated until three weeks after the discontinuance of the use of emetine hydrochloride. Similarly, normal electrocardiograms were obtained at the completion of courses of 14 and 19 grains (0.91 and 1.23 Gm.) of emetine hydrochloride in cases 1 and 4, but subsequent records were demonstrated to be abnormal. In the remaining 5 cases without control records, the first abnormal electrocardiogram was observed from two to seventeen days after the last injection of emetine hydrochloride.

Electrocardiographic Changes.—The commonest electrocardiographic abnormality observed was inversion of the T waves, usually involving all the standard leads. The T waves in leads II and III were inverted in all the cases. The T wave in lead I was isoelectric or inverted in 6 cases, and the T wave in lead IV was inverted in 3 cases. Deviation of the S-T segment was rare, consisting usually in minimal depression; eleva-

Summary of Findings in Nine Patients with Amebic Dysentery Presenting Toxic Effects Following Administration of Emetine Hydrochloride

Case	Age, Yr.	Emetine Hydrochloride: Total Dose, Grains	Emetine Hydrochloride: Dates Given	Toxic Manifestations: Neuromuscular	Cardiac Signs	Electrocardiographic Changes	Time of First Abnormal Electrocardiogram	Duration of Electrocardiographic Change	Other Toxic Symptoms
1 (G. R. M.)	28	18	10/23 to 11/ 5 11/15 to 11/18	Generalized weakness, tremors, dysarthria, dizziness	Dyspnea on mild exertion, palpitation, tachycardia; gallop rhythm; apical systolic murmur	T_1 low; T_2 and T_3 inverted	11/30	5 wk.	Diarrhea and abdominal pain
2 (R. H. B.)	25	22	10/14 to 10/18 10/21 to 11/ 4 11/15 to 11/18	Generalized weakness, most decided in pelvic and shoulder girdles; tremor of hands	Dyspnea and tachycardia on exertion; soft apical systolic murmur	T_1 isoelectric; T_3, T_2 and T_4 inverted; QRS_4 W shaped	11/20	Over 2 mo.	Diarrhea and abdominal pain
3 (E. W.)	30	14	11/ 3 to 11/17	Moderate generalized weakness	Dyspnea on exertion	T_1 and T_4 semi-inverted; T_2 and T_3 deeply inverted and coveplane	12/ 3	Over 5 mo.	
4 (K. H. E.)	29	18	10/20 to 10/24 11/ 6 to 11/19	Weakness of the abductors and adductors, thighs and gluteal muscles	Dyspnea on exertion	T_1 isoelectric, T_2 and T_3 diphasic	12/ 3	2 mo.	
5 (L. S. J.)	30	10	11/14 to 11/24	None	Mild dyspnea on exertion	T_1 flat; T_4 inverted; QRS_2 and QRS_3 W shaped	12/10	Over 2 mo.	
6 (G. K.)	37	15	11/ 1 to 11/10 11/16 to 11/20	Generalized muscular aching and weakness; hyperreflexia, tremor of extremities	None	T_1 low; T_2 and T_3 diphasic	12/14	6 wk.	Diarrhea and abdominal pain
7 (J. M.)	30	10	11/18 to 11/27	None	None	T_1 flat; T_2 diphasic; T_3 inverted	12/10	Over 2 mo.	
8 (K. C.)	26	14	11/ 6 to 11/18	None	Tachycardia on exertion	Small Q_3; T_2 low; T_3 inverted	12/ 5	About 6 wk.	
9 (C. C. A.)	24	7	5/30 to 6/ 6	Generalized weakness, nervousness; tremor of hands	Palpitation, soft apical systolic murmur	T_1 low; T_2 and T_3 inverted	6/ 3	Over 1 mo.	

tion of the S-T segment was not observed. Abnormalities in the QRS complex occurred in 2 cases and consisted in deep Q waves in leads II and III in 1 case and a W-shaped QRS complex in lead IV in the second case. Prolongation of the P-R interval or significant cardiac arrhythmia was not observed.

The duration of the abnormal findings varied considerably but was usually prolonged. In 3 cases the electrocardiogram returned to normal from four to six weeks after the abnormalities were first noted, and in 2 the abnormalities disappeared after two months. The other patients evacuated from the hospital after periods varying from one to four months still had abnormal records at the time of transfer.

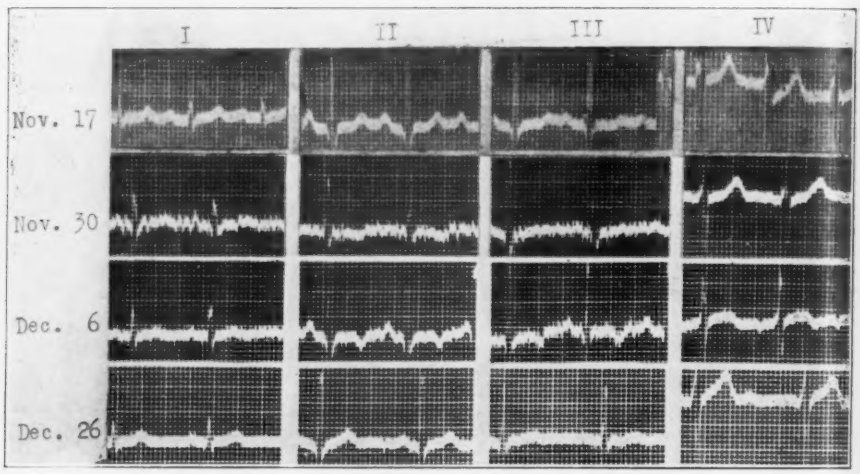

Fig. 1 (case 1).—The patient, Sgt. G. R. M., aged 28, had amebic dysentery treated with emetine hydrochloride, 18 grains (1.16 Gm.) intramuscularly, 1 grain daily from October 23 to November 5 and from November 15 to 18. The electrocardiogram shows lowering of the T waves in leads I and IV and deep inversion of the T waves in leads II and III. By December 26 the record had returned to normal. Note the artefacts on November 30 and December 6 produced by the patient's muscular tremor.

Cardiac Examination.—Generally the clinical examination of the cardiovascular system was not strikingly abnormal. Moderate tachycardia in patients at rest and after mild effort was observed in 3 cases, and in 1 (case 1) it was associated with presystolic gallop rhythm. Mild precordial discomfort occurred in 1 patient, and dyspnea and fatigue on exertion of various degrees were a presenting symptom in 5 instances. None of the patients showed any abnormality in the size or configuration of the heart by roentgenologic examination. No significant lowering of the blood pressure was noted in this series.

Neuromuscular Manifestations.—Generalized muscular weakness and tremor, involving particularly the lower extremities, developed in 5 patients. In 1 patient (case 1) the neuromuscular weakness was incapacitating and was manifested by decided coarse tremor of the extremities, lips and tongue, difficulty in speech, weakness of the upper and lower extremities and generalized hyperreflexia. The patient in case 2 exhibited similar abnormalities, but they were of lesser severity.

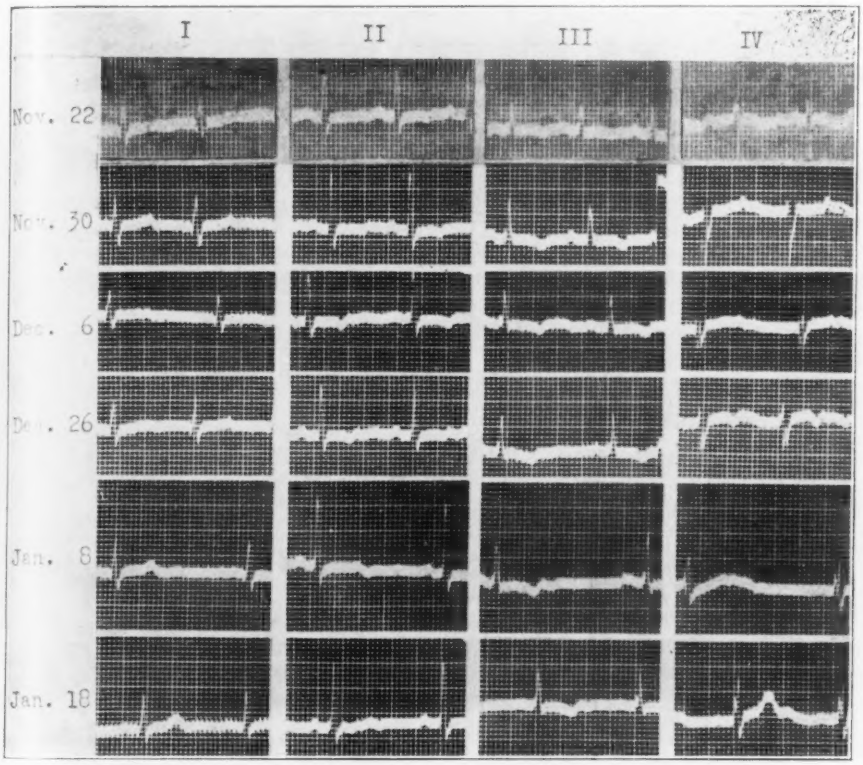

Fig. 2 (case 2).—The patient, Pvt. R. H. B., aged 25, had amebic dysentery treated with emetine hydrochloride, 22 grains intramuscularly, 1 grain daily from October 14 to 18, October 21 to November 4 and November 15 to 18. The electrocardiogram shows isoelectric T waves in lead I, inverted T waves in leads II, III and IV, a small R wave in lead IV and a polyphasic QRS complex. The record of January 18 is normal except for slight lowering of the T wave in lead II and inverted T wave in lead III.

Three other patients complained of generalized weakness, but there were less striking objective findings. Abnormal reflexes or sensory changes were not observed.

Gastrointestinal Symptoms.—In 3 instances, nonbloody diarrhea recurred during the course of treatment in association with neuromuscular symptoms of toxicity. There was cramping abdominal pain in each instance. No further antiamebic therapy was administered to the patients, and the symptoms disappeared spontaneously when the use of emetine hydrochloride was discontinued.

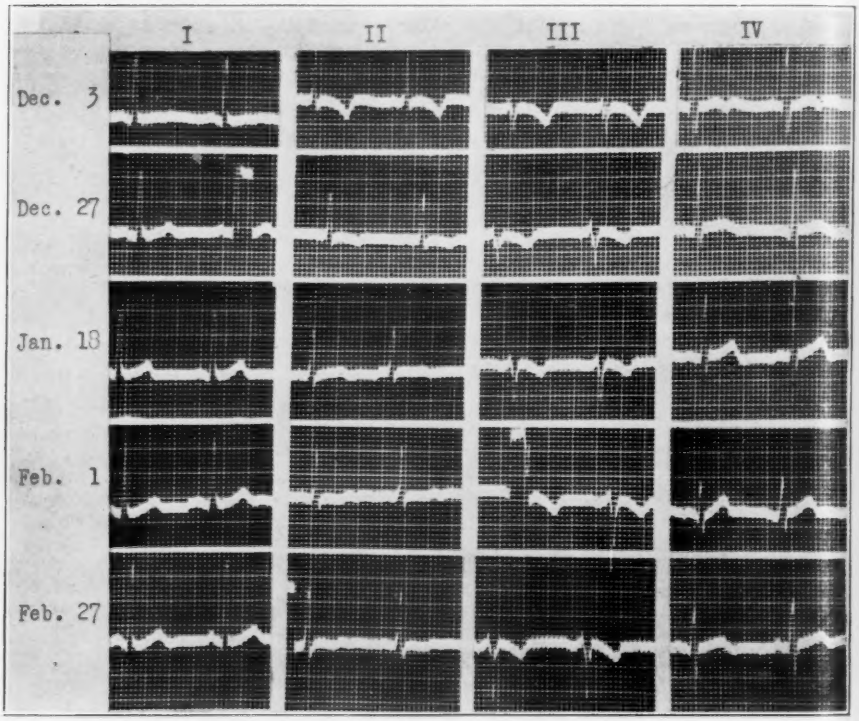

Fig. 3 (case 3).—The patient, Pvt. E. W., aged 30, had amebic dysentery treated with emetine hydrochloride, 14 grains intramuscularly, 1 grain daily from November 3 to 17. The electrocardiogram shows a low T wave in lead I, deeply inverted T waves in leads II and III and a diphasic T wave in lead IV. A semi-inverted T wave in lead II and an inverted T wave in lead III are still present on February 27.

COMMENT

It is evident from the cases presented that electrocardiographic changes, clinical signs of cardiac damage and neuromuscular disturbances occur not infrequently after the administration of emetine hydrochloride. The electrocardiograms in our cases were generally obtained at the end of the course of treatment or from several days to two weeks

after the last injection. It is probable that had more frequent records been obtained during the course of treatment electrocardiographic changes would have been demonstrated oftener. We have recently treated 3 additional patients with emetine hydrochloride and have demonstrated electrocardiographic changes in the form of inversion of the T waves after administration of a total of 5 and 6 grains (0.32 and 0.39 Gm.). Use of the drug was promptly discontinued, and the abnormalities disappeared within one to two weeks.

Although electrocardiographic changes may occur after administration of as little as 3 or 4 grains (0.19 or 0.26 Gm.) of emetine hydrochloride, we were struck by the fact that at times they did not appear

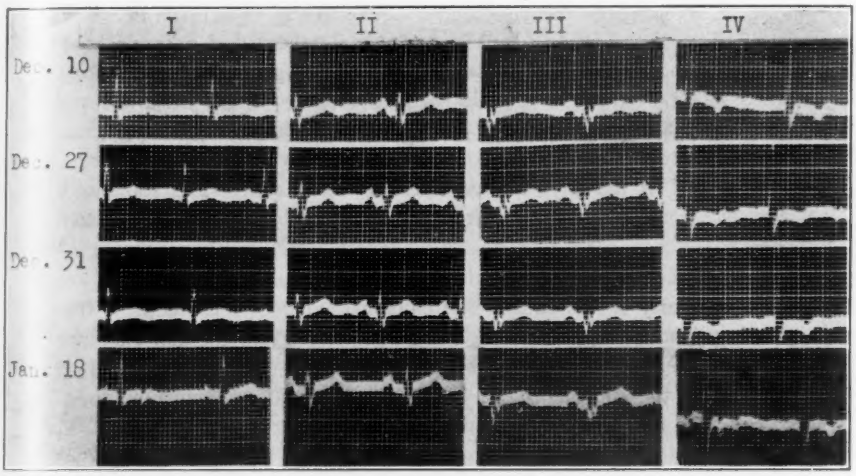

Fig. 4 (case 5).—The patient, Pfc. L. J., aged 30, had amebic dysentery treated with emetine hydrochloride, 10 grains intramuscularly, 1 grain daily from November 14 to 23. The electrocardiogram shows a low T wave in lead I, an inverted T wave in lead IV and a polyphasic W-shaped QRS complex in leads II and III. The abnormal T wave in lead IV and QRS complex are still present on January 18.

until the entire course had been completed. In 3 of the cases an electrocardiogram was normal after 12, 14 and 19 grains (0.78, 0.91 and 1.23 Gm.) of emetine hydrochloride respectively were administered, but a record obtained one to two weeks after the cessation of treatment presented distinct changes. Thus there may be a lag in the time of the appearance of the electrocardiographic abnormalities, and the absence of such changes cannot always be utilized as a criterion for the continued administration of emetine hydrochloride with impunity beyond a certain level of dosage. Were one to wait until electrocardiographic changes developed before discontinuing the drug, increased damage would result.

The appearance of tachycardia, fatigue or dyspnea on exertion, muscular weakness, tremor or any other toxic manifestation is an indication for the immediate discontinuance of emetine hydrochloride therapy, even in the presence of a normal electrocardiogram.

Another interesting observation in our cases was the relatively long duration of electrocardiographic abnormalities. In one half the cases the abnormalities persisted for two months or more after the cessation of treatment, and in no case was the duration less than one month. This suggests either that the emetine hydrochloride is fixed in the myocardium for a long period or that the toxic myocardial changes that it produces are on an anatomic basis. The underlying cause for the electrocardiographic changes and cardiac damage is probably myocardial degeneration. This has been demonstrated in experiments on animals in which depression of the cardiac muscle and actual myocardial necrosis have been observed, particularly after large doses or prolonged administration.[7] The electrocardiographic changes which we have described are nonspecific and resemble those seen in toxic, inflammatory or degenerative myocardial states due to other causes. In view of these findings, the interval of ten days to two weeks between courses, as sometimes advised, seems too brief, and it would be advisable to wait one to two months after a course of emetine hydrochloride has been completed before the course is repeated. If electrocardiographic changes are observed early in the course of treatment and use of the drug is discontinued immediately, there is reason to believe that the abnormalities disappear more rapidly and clinical toxic changes do not develop. This emphasizes the importance of frequent electrocardiograms during administration of emetine hydrochloride.

The dose required to produce toxic reactions varied in this series. This suggests that there is considerable variation in tolerance to the drug that can be ascribed to individual differences either in rate of excretion or in susceptibility. It has also been demonstrated in the past that different commercial preparations of emetine hydrochloride vary considerably in toxicity. This has been attributed by some to the presence in the preparation of a toxic product such as cephalin.[3] In the present series of cases it is known that a variety of commercial preparations were involved and that the incidence of toxic reactions cannot be ascribed to a single toxic preparation.

The cases presented in this report emphasize also the importance of differentiating between the diarrhea produced by the amebic dysentery

7. Ghosh, B. N., and Adhya, P. C.: Some Newer Observations on the Pharmacology of Emetine, J. Indian M. A. **13**:37, 1943; abstracted, Trop. Dis. Bull. **41**:289, 1944. Scherf.[2] Levy and Rowntree.[1] Boyd and Sollmann.[4]

and that produced as a result of the administration of emetine hydrochloride. In several of the cases, the recurrence of diarrhea either during or shortly after the completion of a course of emetine hydrochloride was interpreted as being due to a recurrence of the disease and further antiamebic treatment was deemed indicated. In each instance the diarrhea subsided spontaneously when treatment with the drug was discontinued. In most cases of true amebic dysentery improvement in the diarrhea is noted during the early phase of treatment; recurrence of diarrhea later in the course should lead one to suspect that this might be ascribed to the toxic effect of emetine hydrochloride.

The following regimen is recommended during the administration of emetine hydrochloride. It is our belief that the frequency of serious toxic manifestations would be decreased if it is followed. 1. The patient should be maintained on absolute rest in bed throughout the course of treatment. The importance of this is demonstrated by the patients in cases 1 and 2, who fainted or collapsed while walking in the area of the hospital. 2. The pulse rate should be recorded at frequent intervals daily and preferably graphed on the clinical record. Tachycardia may be the first clinical sign of toxic effect on the heart. 3. The patient should be examined and questioned at least daily for the detection of signs of toxicity such as diarrhea, fatigue, dyspnea on exertion, muscular tremors or weakness and dizziness. 4. It is advised that an electrocardiogram be taken before treatment is instituted and after the fifth grain. Another electrocardiogram should be obtained at the completion of the course of treatment and again one week later. Use of the drug should be promptly discontinued if significant changes are found. 5. It has been our clinical impression that in the majority of cases of amebic dysentery as great a therapeutic effect has resulted from the administration of 5 to 7 grains (0.32 to 0.45 Gm.) of emetine hydrochloride as has been obtained with higher doses sometimes recommended. 6. If clinical evidence of amebiasis persists after the first course of treatment and no evidence of toxicity of emetine hydrochloride has been observed, a rest period of at least a month should intervene prior to the resumption of treatment. If significant electrocardiographic changes or other clinical evidence of toxicity are observed during or after the first course of treatment with emetine hydrochloride, at least two months should be allowed to intervene before further emetine hydrochloride is administered. If that becomes necessary, electrocardiographic tracings should be made after the third grain is given. It would seem to be safer to resort to other forms of treatment for this group of patients. 7. Emetine hydrochloride should not be used in the presence of suspected organic heart disease and should be used with great caution in patients who are anemic and debilitated.

CONCLUSIONS

1. Nine cases of amebic dysentery are presented in which toxic cardiac manifestations developed after treatment with emetine hydrochloride in total doses varying from 7 to 22 grains (0.32 to 1.42 Gm.). These consisted in fatigue, dyspnea and tachycardia on mild exertion and electrocardiographic abnormalities generally involving the T waves in all leads.

2. The dose of emetine hydrochloride required to produce toxic cardiac effects varied in each case, suggesting individual differences in susceptibility or in rate of excretion of the drug.

3. The time of appearance of the electrocardiographic abnormalities also varied in each case and was often delayed until one or two weeks following the discontinuation of treatment. Owing to this lag in the appearance of electrocardiographic changes, their absence cannot be safely utilized as a criterion for the continuation of emetine hydrochloride therapy beyond a certain dose.

4. The electrocardiographic abnormalities, when present, were of long duration, often persisting for two months or more following cessation of treatment, suggesting prolonged fixation of the drug in the myocardium or actual myocardial degeneration as the basis for the cardiac manifestations.

5. Toxic effects on the neuromuscular and gastrointestinal systems generally preceded the appearance of toxic cardiac effects. The former as well as the latter are indications for the discontinuance of further therapy with emetine hydrochloride.

6. A regimen is outlined for the management of amebic dysentery when emetine hydrochloride is employed, which, it is believed, will reduce the danger of toxic cardiac effects.

PENICILLIN IN THE TREATMENT OF KERATOSIS BLENNORRHAGICA WITH POLYARTHRITIS

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THE PURPOSE of this communication is to present our observations on 3 cases of keratosis blennorrhagica treated with penicillin. To our knowledge, no record of this type of therapy for keratosis blennorrhagica has appeared so far in the literature. It is a rare condition, occurring approximately in the ratio of 1 in every 5,000 to 7,500 cases of gonorrhea.[1] To date, somewhat over 100 cases have been reported.

Many excellent reviews[2] of this disease have been published, and we shall not go into a detailed description of the lesions. The clinical syndrome is characterized by the triad of urethritis, arthritis and dermatosis.[3] The onset is insidious and follows chronic and recurrent attacks of gonorrheal urethritis. Chills and fever are present. The dermatitis is usually preceded by or associated with arthritis involving one or several joints. The lesions of the skin consist of vesicles, pustules and crusting associated with keratosis. The nails are commonly affected by pustules which develop under the distal portions. The pustules dry, forming hyperkeratotic crusts, which become heaped up and separate the nails from their beds.

REPORT OF CASES

CASE 1.—R. B., a 27 year old unmarried Negro man, was admitted to Bellevue Hospital on Oct. 5, 1944, complaining of "sores" on his fingers, hands, toes, feet,

From the Fourth Medical Service (New York University College of Medicine), Bellevue Hospital and the Medical Service, Meadowbrook Hospital.

1. Combes, F. C.; Dietrich, C., and Cohen, J.: Keratosis Blennorrhagica: A Brief Review and Report on the Effects of Hyperpyrexia in Its Treatment, J. A. M. A. **114**:2078-2082 (May 25) 1940.

2. Herold, W. C., and Smith, D. C.: Keratosis Blennorrhagica: Report of Two Cases, Arch. Dermat. & Syph. **44**:398-408 (Sept.) 1941. Epstein, E.: Differential Diagnosis of Keratosis Blennorhagica and Psoriasis Arythropathica, ibid. **40**:547-559 (Oct.) 1939. Combes and others.[1]

3. Downing, J. C.: Keratoderma Blennorrhagicum: Report of a Case, J. A. M. A. **102**:829-831 (March 17) 1934.

legs and scalp for three weeks, during which time all the nails had fallen off his fingers and toes. Simultaneously, his right knee had become swollen and painful.

In 1938, three days after sexual exposure, he noticed a urethral discharge. Several days later pain and swelling of the left wrist and hand appeared. At another hospital, gonorrheal urethritis and gonorrheal arthritis were diagnosed and treated with sulfonamide compounds. The discharge disappeared promptly, and

Fig. 1 (case 1).—Keratosis blennorrhagica showing typical lesions of the skin of hands and feet.

the arthritis improved. Since that time the patient has required hospital care on six different occasions for recurrence of pains and swelling of the joints, accompanied each time with a urethral discharge. In 1942 he was treated for conditions of the skin similar to those for which he was admitted to this hospital. After eleven months of hospitalization and varied treatment, the skin slowly cleared until there was no residuum.

He denied any sexual exposure since 1938. He stated that various joints had been involved during all the stages of his illness, including both knees, the left foot and both elbows and wrists.

The systemic review revealed no abnormalties, and the past history, other than that mentioned, was not pertinent. The family history was noncontributory.

Physical examination revealed a well nourished and well developed young Negro man with typical lesions of the skin of both hands and feet, involving all the fingers and toes (fig. 1). Lesions were present also on both legs, on the abdomen and on the scalp. All the nails of his fingers and toes had fallen off. The dermatitis consisted of discrete, hyperkeratotic papules and vesicles varying from 0.5 to 5 cm. in diameter. Some showed secondary infection with formation of pus.

The right knee was moderately swollen, warm and sore on pressure and on motion. Rectal examination revealed the prostate to be soft, boggy and tender, particularly over the median lobe. The remainder of the physical examination revealed normality.

The white blood cell count was 14,000 per cubic millimeter on his admission to the hospital and became normal with treatment. Examination of the urine showed no abnormalities. The Wassermann and Frei tests elicited negative reactions. The erythrocyte sedimentation rate was 19.0 mm. in one hour (Westergren). Prostatic massage yielded no fluid. Complement fixation tests for Gonococcus in the blood and in fluid obtained from the right knee elicited strongly positive reactions. Culture of the fluid from the right knee was sterile. Chemical examination of the blood showed 10.0 mg. of calcium, 2.03 mg. of phosphorus and 2.5 mg. of uric acid per hundred cubic centimeters. The acid phosphatase content was 3.8 units, and the alkaline phosphatase content was 3.1 units per hundred cubic centimeters. Culture of the pus from one of the lesions on the skin yielded Staphylococcus aureus. Consultation with the department of dermatology confirmed the diagnosis of keratosis blennorrhagica.

The temperature on admission was 100.6 F. and remained at this level until the ninth day in hospital, when penicillin therapy was instituted. The penicillin was administered intramuscularly, 10,000 units every three hours, day and night, for a total dose of 1,500,000 units. Before administration of penicillin was started, compresses of potassium permanganate were used. They partially cleared up the secondary infection of the skin.

The response to penicillin was good. Shortly after treatment was begun, the temperature fell to normal and remained so until the patient's discharge from the hospital. All pustular involvement of the skin disappeared promptly. The keratotic lesions resolved slowly, and no new ones formed. The hyperkeratotic crusts fell off and were slowly replaced by normal skin. Up to the time of discharge the nails had not yet grown back. A few minimal keratotic residua were still present on the extremities. The effusion of the knee joint, removed by tapping before penicillin therapy, did not return. Pain and tenderness of the joint were abolished and did not recur. The patient was discharged from the hospital on the twenty-fourth day. All efforts to contact him a year later for follow-up were unsuccessful.

CASE 2.—P. K., a 36 year old white man, was admitted to Meadowbrook Hospital on Aug. 23, 1944, with pain in the left knee and both wrists and an eruption on the wrists, which became slightly swollen. The fingers were stiff, and he was unable to move them. These complaints were followed by stiffness and pain in the left knee. At about the same time as the joints became involved

the rash appeared. He gave a history of two episodes of gonorrheal urethritis, the first at the age of 29 and the other at 30. The remainder of the history was irrelevant.

Physical examination revealed a well developed, well nourished white man who appeared chronically ill. The blood pressure was 160 systolic and 100 diastolic. The heart was not enlarged. The sounds were of good quality, and there were no murmurs. The remainder of the physical examination showed nothing abnormal excepting the extremities. There was severe pain on movement of the fingers, wrists and the left knee. The wrists were slightly swollen. Both legs were covered with many pustular lesions, which were also present on the buttocks.

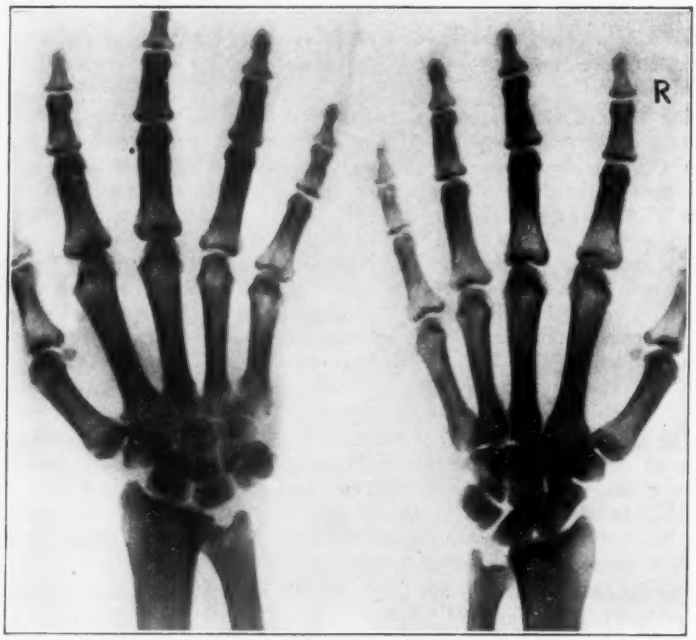

Fig. 2 (case 2).—Diffuse osteoporosis in the region of the carpal and metacarpal bones of the left hand and wrist, with narrowing of the spaces between the joints.

The blood cell count on admission showed a hemoglobin content of 82.2 per cent and a white blood cell count of 14,400, with 76 per cent polymorphonuclears, 22 per cent lymphocytes and 2 per cent monocytes. The white cell count was repeated on five occasions and varied between 8,100 and 18,200. The platelets numbered 310,000 per cubic millimeter. The nonprotein nitrogen content was 17 mg., the creatinine content 1.5 mg. and the sugar level 85 mg. per hundred cubic centimeters. The alkaline phosphatase content was 9.0 units and the acid phosphatase content 2.5 units per hundred cubic centimeters. The serum albumin-globulin ratio showed an inversion, with the albumin 3.7 Gm. and the globulin 5.1 Gm. per

hundred cubic centimeters. The result of the cephalin flocculation test was reported as positive (1 plus). The Wassermann and Kahn tests on the blood serum elicited negative reactions, and two cultures of the blood showed no growth. The sedimentation rate at intervals varied between 30 and 35 mm. in one hour (Cutler). Cultures taken from the lesions of the skin revealed no growth, and examination of prostatic smears gave normal results. Roentgenograms of the knee joints did not reveal any abnormality of the bones or joints; the hands showed diffuse

Fig. 3 (case 2).—Keratosis blennorhagica showing typical lesions of the skin of hands and feet.

osteoporosis in the region of the carpal bones and the adjacent portions of the metacarpals of the left hand and wrist, with narrowing of the spaces between the joints (fig. 2).

The temperature on his admission to the hospital was 100.8 F. and ranged between 99.5 and 102.5 F. The lesions of the skin spread to his hands and feet and involved the nails (fig. 3). The pains in the joints persisted, and movement provoked great discomfort. He was given large doses of salicylates, without relief of the pains in the joints.

On Sept. 28, 1944 administration of sulfadiazine was started, and a total of 20 Gm. was administered, without any response, the temperature remaining between 99.5 and 101.5 F.

On October 2 penicillin therapy was instituted. He received 10,000 units intramuscularly every three hours for a total of 100,000 units. On October 5 the dose was increased to 20,000 units every four hours for seven doses. The total

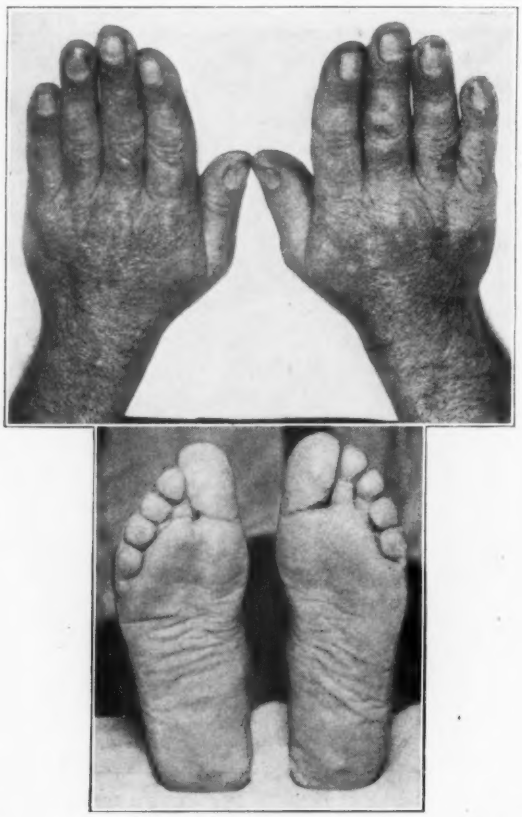

Fig. 4 (case 2).—Appearance of hands and feet one year after penicillin therapy.

amount of penicillin used was 240,000 units. On October 12 it was noted that the arthralgia and swelling of the joints had disappeared. The legs had improved, and his general condition was much better. The temperature had dropped to normal and remained there until the date of discharge.

The patient was seen again on Oct. 7, 1945, one year after his discharge from the hospital, for a follow-up examination. He stated that he continued to feel well after leaving the hospital. All the nails of his fingers and toes had fallen

off and had gradually been replaced by normal nails and tissues. Only a few pigmented areas could be seen on the feet (fig. 4). His only complaint was stiffness of the last three fingers of the left hand and soreness and swelling of the manubriosternal area. This joint was tender on palpation and felt enlarged. He was working as a truck driver and had not missed any time from work.

Roentgenograms of the hands and of the sternum at this time revealed a recalcification of the bones of the carpus, together with a discreteness of the carpal joints and carpal-metacarpal articulation, almost normal in appearance.

The manubriosternal articulation showed proliferative changes, with thickening of the periosteum for 2 inches (5 cm.) along the posterior surface of the articu-

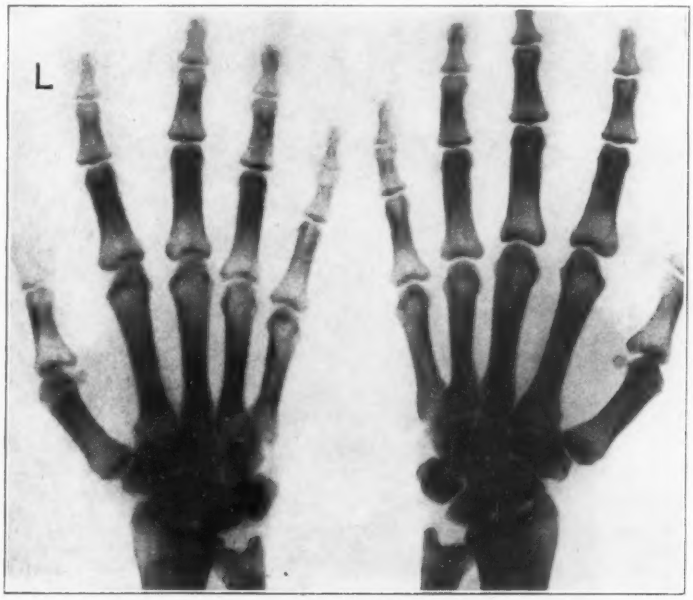

Fig. 5 (case 2).—Recalcification of the bones of the carpus and a discreteness of the carpal joints and carpal-metacarpal articulation.

lating bones. Numerous erosions of the articulating margins were noticeable (figs. 5 and 6).

CASE 3.—A. G., a 32 year old white man, was admitted to Bellevue Hospital on June 6, 1944, complaining of pain "in all the joints" and a generalized cutaneous eruption lasting for about a year. On four previous occasions he had been admitted for the same complaints. The first attack of articular pain and swelling occurred in 1930, starting in the feet and spreading to almost all the joints of the body. Several weeks after the onset of polyarthritis a generalized cutaneous eruption developed. At this time a urethral discharge occurred, but gonococci were not demonstrated. The attack lasted fourteen months and was associated with chills and fever. He was symptom free after that period and had no residual manifestations of the joints or skin. In 1933 he suffered a similar attack of poly-

arthritis, without cutaneous manifestations. In 1935 there was a recurrence, similar to the first attack, with pains in the joints, fever and eruption of the skin. He was asymptomatic until April 1943, when he had his severest attack. At this time he had fever and polyarthritis for six weeks and a generalized cutaneous eruption for one week. He was acutely ill and suffered severe pains in the joints. He was treated for several weeks with vitamin A but showed only slight improvement. He then received a prolonged course of sulfonamide drugs, with little response. He signed out of the hospital, against advice, after one month. At this admission, one year later, he had grown progressively worse and was unable

Fig. 6 (case 2).—The manubriosternal articulation shows proliferative changes, with thickening of the periosteum.

to move. During that time he had experienced repeated shaking chills and fever. Almost all the peripheral joints showed contractures or deformity, and the generalized cutaneous eruption had grown worse. He was a complete invalid.

Physical examination revealed an acutely ill, emaciated and cachectic white man. There were flexion deformities of the hands, arms and legs. The wrists, elbows and knees were swollen, hot and tender. He was unable to move any of these joints. Over the arms, legs and pelvic regions there was an eruption of the skin, composed of dry, scaly, erythematous papules and circular patches. The finger nails and toe nails showed destructive changes (fig. 7). The remainder

of the physical examination disclosed no unusual condition. There was no urethral discharge.

The temperature varied between 100 and 103 F. The leukocyte count ranged from 10,200 to 20,000. The red blood cell count revealed moderate anemia. Analysis of the urine showed no abnormalities. Urethral culture failed to demon-

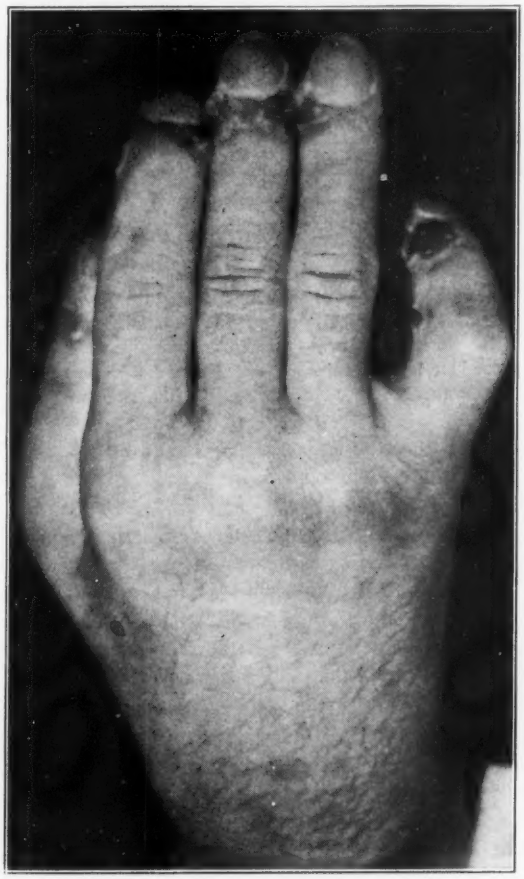

Fig. 7 (case 3).—Keratosis blennorrhagica showing typical lesions of the skin.

strate gonococci. The Wassermann reaction was negative, and the blood uric acid content was normal. Fluid obtained by tapping the knee contained 160,000 neutrophils per cubic millimeter, but culture of this material was sterile.

The patient was given rest in bed and treated symptomatically. During his stay in the hospital he remained bedridden and unable to move without pain. He again signed out, against advice, before penicillin therapy could be instituted.

On his final admission, on July 21, 1945, the patient was hospitalized in the Dermatology Service.[4] His complaints were severe pains in the joints and a generalized cutaneous eruption which had continued since his previous admission. He had been bedridden since he left the hospital and had lost a considerable amount of weight. His appetite was poor, and he suffered intermittent diarrhea.

On physical examination he was emaciated and chronically ill. He lay motionless in bed, with his knees drawn up, unable to move without severe pain in all his joints. The skin of the extremities and the trunk was covered with crusting and scaling lesions. The fingers were stiff, and there was ankylosis of the knees and wrists, with atrophy of the periarticular soft tissues. The white blood cell count was 28,000 per cubic millimeter, with 80 per cent polymorphonuclears and 20 per cent lymphocytes. The red blood cells numbered 3,100,000 per cubic millimeter, and the hemoglobin content was 60 per cent. The temperature ranged from 100 to 102 F. for thirteen days and rose terminally to 106 F.

The patient was given general supportive therapy. He required considerable sedation with codeine and Demerol (1-methyl-4 phenyl piperidine 4-carbonic acid) because of the pain in the joints. He received activated viosterol, ferrous sulfate and dried yeast. On the third day in the hospital penicillin therapy was started. He received 40,000 units every three hours for a total of 1,440,000 units. Despite the treatment he became progressively worse. He became incontinent and refused to eat. Several infusions of dextrose, amigen and plasma were given, without any noticeable effect. He became confused, disoriented and incoherent and died on the fourteenth day in the hospital. The lesions of the skin and arthritis remained unchanged.

Permission for postmortem examination was refused.

COMMENT

The cases described meet the three criteria for a diagnosis of keratosis blennorrhagica: gonorrhea, arthritis and the characteristic cutaneous lesions.[1] Active urethritis is not essential. A history of previous gonorrheal infection (single or repeated) or evidence of definite pathologic changes in the genitourinary tract which are probably gonorrheal is said to fulfil the diagnostic requirement.[5]

Many forms of treatment have been advocated in the past, based on limited experience by various investigators. Local treatment is of little value. Surgical measures, such as drainage of foci in the prostate and seminal vesiculectomy, have been used. Autogenous vaccines were stated to be helpful.[5] Chemotherapy, in the form of administration of sulfanilamide and sulfarsphenamine, has been used, with indeterminate and inconsistent results.[1] Fever therapy by various means has been advocated.[6] Recently, large doses of vitamin A have been found effective.[7]

4. Dr. Frank C. Combes permitted us to include the final chapter in the history of this patient.

5. Scholtz, M.: A Syndrome of Blennorrhagic Keratoderma: Report of a Case, Arch. Dermat. & Syph. **15**:165-170 (Feb.) 1927.

Some of these patients present a chronic progressive cutaneous and articular disease, which in the past has continued relentlessly in spite of all previous methods of treatment, as in case 3. Often the disease is subject to natural remissions and recurrences, which make it difficult to evaluate conclusively any therapy not based on its employment in a large group of patients followed for a long time.

The effectiveness of any treatment in this disease must be gaged by its influence on the important manifestations: (1) the urethritis, (2) the arthritis, (3) the cutaneous eruption or keratosis and (4) the usual secondary infection of the lesions of the skin. Urethritis or a genitourinary focus was not demonstrable in our cases, but truly specific therapy would be expected to eradicate it when present. The arthritis resolved spontaneously in case 1 before penicillin therapy was begun. In case 2, the arthralgia and arthritis, although unrelieved by administration of salicylates, responded rapidly during penicillin therapy.

The cutaneous eruption and probably the secondary infection are apt to prove most resistant to treatment in the average case. The dermal suppuration was abolished with striking rapidity in cases 1 and 2. The keratotic lesions showed a therapeutic response which, even though not complete, surpassed the results from other measures reported.

The patient in case 2 required a much smaller amount of penicillin than the patient in case 1 for a favorable response. No definite statement, therefore, can be made as to the total dose to be given as a rule. Apparently it will have to be regulated individually according to the severity and responsiveness of the disease.

Final conclusions as to the value of use of penicillin in keratosis blennorrhagica cannot be drawn from these cases. The rarity of this condition makes it impossible for one group of investigators to assess properly any form of treatment. The early, thorough use of sulfonamide drugs and penicillin in the treatment of gonorrhea may reduce the incidence of this disease even further. The tendency to spontaneous remissions and recurrences in many of the cases emphasizes the need for cautious evaluation of any method of treatment unless employed in an adequate number of cases. The accumulation of further experience

6. (*a*) Epstein, E.: Hyperpyrexia in the Treatment of Keratoderma Blennorrhagicum, Am. J. Syph., Gonor. & Ven. Dis. **21**:148-154 (March) 1937. (*b*) Epstein, E., and Chambers, S. O.: Keratosis Blennorrhagica with Corneal Lesions: Further Observations on the Therapeutic Effect of Hyperpyrexia, Arch. Dermat. & Syph. **36**:1044-1051 (Nov.) 1937. (*c*) Combes and others.[1]

7. Combes, F., and Behrman, H.: Use of Vitamin A in Keratosis Blennorrhagica: Successful Treatment with Massive Doses; Report of a Case, Arch. Dermat. & Syph. **46**:728-733 (Nov.) 1942.

revealed in the literature should lead to reliable evaluation of the use of penicillin in the treatment of keratosis blennorrhagica.

Some similarities exist between this disease and so-called Reiter's syndrome. In 1916 Reiter [8] described a clinical picture characterized by the triad: urethritis, arthritis and conjunctivitis. He demonstrated a spirochete in the blood of his patient and called it "Spirochaeta forans." Since then, no spirochete or any other specific organisms have been found in any of the cases. According to the present consensus, the urethritis is felt to be nonspecific in character and is not venereal in cause. The arthritis may involve only one joint, but in most cases it is polyarticular.

Lesions of the skin similar to those seen in keratosis blennorrhagica have been observed in Reiter's syndrome.[9] Lever and Crawford [10] have reported a case of keratosis blennorrhagica without gonorrhea which they felt might be a case of Reiter's disease. Conversely, cases of keratosis blennorrhagica have been reported [11] in which involvement of the eyes was present in addition to urethritis, arthritis and dermatitis.

The exact relationship between these two rather ill defined syndromes is not clear and remains open for further study. It is conceivable and worthy of consideration in any new investigation of this subject that Reiter's syndrome may be a variation of the classic clinical picture of keratosis blennorrhagica. The chief distinction at the present time is the widespread acceptance of the latter condition as gonorrheal in origin, while Reiter's syndrome is regarded as nonvenereal. The difference may well be resolved by future proof that gonorrheal infection in keratosis blennorrragica occurs as a coincidental factor or acts as a predisposing agent in the causative process, actually producing pictures of both diseases and their variants.

CONCLUSIONS

Three cases of keratosis blennorrhagica are described. In 2 of the patients, treatment with penicillin gave a rapid and satisfactory response. The third patient did not submit to penicillin therapy until he was in a terminal state. Although our experience with the treatment has been impressive, the need for more extensive therapeutic study before final conclusions are drawn is emphasized.

8. Reiter, H.: Ueber eine bisher unerkannte Spirochäteninfektion (Spirochaetosis arthritica), Deutsche med. Wchnschr. **42**:1535, 1916.

9. Hollander, J. L.; Fogarty, C. W., Jr.; Abrams, N. R., and Kydd, D. M.: Arthritis Resembling Reiter's Syndrome: Observations on Twenty-Five Cases, J. A. M. A. **129**:593-595 (Oct. 27) 1945.

10. Lever, W. F., and Crawford, G. M.: Keratosis Blennorrhagica Without Gonorrhea (Reiter's Disease?), Arch. Dermat. & Syph. **49**:389-397 (June) 1944.

11. Chambers, S. O., and Koetter, G. F.: Keratosis Blennorrhagica, Arch. Dermat. & Syph. **27**:411-420 (March) 1933. Combes and others.[1]

News and Comment

THE ELLA SACHS PLOTZ FOUNDATION FOR THE ADVANCEMENT OF SCIENTIFIC INVESTIGATION

During the last year forty applications for grants were received by the Trustees of the Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation, of which twenty-nine came from the United States and the other eleven from seven different countries in Europe, Asia and North and South America.

In the twenty-three years of its existence the Foundation has made five hundred and fifty-one grants, which have been distributed to scientists throughout the world.

In their first statement regarding the purposes for which the Fund would be used, the Trustees expressed themselves as follows:

1. For the present, researches will be favored that are directed toward the solution of problems in medicine and surgery or in branches of science bearing on medicine and surgery.
2. As a rule, preference will be given to researches on a single problem or on closely allied problems; it is hoped that investigators in this and in other countries may be found whose work on similar or related problems may be assisted so that more rapid progress may be made possible.
3. Grants may be used for the purchase of apparatus and supplies that are needed for special investigations and for the payment of unusual expenses incident to such investigations, including technical assistance, but not for providing apparatus or materials which are ordinarily a part of laboratory equipment. Stipends for the support of investigators will be granted only under exceptional circumstances.

In the past few years the policy outlined in paragraph 2 of the Trustees' statement has been neglected, and grants will be given in the sciences closely related to medicine without reference to special fields. The maximum size of grants will usually be less than $500.

Applications for grants to be held during the year 1947-1948 must be in the hands of the Executive Committee before April 15, 1947. There are no formal application blanks, but letters asking for aid must state definitely the qualifications of the investigator, give an accurate description of the research and state the size of the grant requested and the specific use of the money to be expended. In their requests for aid applicants should state whether or not they have approached other foundations for financial assistance and what other sources of support are relied on for research. It is highly desirable to include letters of recommendation from the directors of the departments in which the work is to be done. Only applicants complying with these conditions will be considered.

Applications should be sent to Dr. Joseph C. Aub, Massachusetts General Hospital, Fruit Street, Boston 14, Massachusetts, U. S. A.

THE FOURTH INTERNATIONAL CANCER RESEARCH CONGRESS

The Fourth International Cancer Research Congress will be held in St. Louis, Sept. 2 to 7, 1947. The Union International Contre le Cancer having accepted the invitation of the American Association for Cancer Research, the Congress will be held under the joint auspices of these two organizations, with Dr. E. V. Cowdry, Professor of Anatomy of the Washington University School of Medicine and Director of Research of the Barnard Free Skin and Cancer Hospital, serving as President of the Congress.

Of the previous congresses, the first was held in Madrid, Spain, in 1933; the second in Brussels, Belgium, in 1936, and the third in Atlantic City, N. J., in 1939. Because of the recent war there has not been a congress during the past eight years.

The State Department in Washington having approved of the International Cancer Research Congress, official invitations soon will be sent to all foreign governments who are to send delegates.

Initial steps in the organization of the Congress have been completed, in that all officers and committees have been appointed and are enthusiastically at work. In addition to the President, Dr. E. V. Cowdry, Dr. J. Godard, President of the Union Internationale Contre le Cancer, and Dr. W. U. Gardner, President of the American Association of Cancer Research, will serve ex officio as members of the Executive Committee.

The following men have accepted chairmanships: A. N. Arneson, St. Louis (Local Arrangements); S. Bayne-Jones, New Haven, Conn. (Finance); C. W. Larimore, New York (Exhibits); L. A. Scheele, Bethesda, Md. (Government Liaison); M. G. Seelig, St. Louis (Publicity), and Shields Warren, Boston (Program).

Headquarters will be at the Hotel Jefferson, St. Louis, where some three hundred rooms will be available for guests. Moreover, other nearby hotels in St. Louis have signified a willingness to make reservations on advance notification by those contemplating attendance at the Congress.

American Society for the Study of Sterility.—The third annual convention of the American Society for the Study of Sterility will be held at the Hotel Strand, Atlantic City, N. J., on June 7 and 8, 1947, preceding the annual session of the American Medical Association. The general purpose of the meetings will be to convey to the physicians treating marital infertility an over-all picture of the latest advances in reproduction. The program will include original papers, round table discussions, scientific exhibits and personal demonstrations. The sessions will be open to all members of the medical and allied professions. Additional information may be obtained from the secretary, Dr. John O. Haman, 490 Post Street, San Francisco 2, Calif.